

AP



(12) **EUROPEAN PATENT SPECIFICATION**

- | | |
|---|---|
| <p>(45) Date of publication and mention of the grant of the patent:
 19.08.1998 Bulletin 1998/34</p> <p>(21) Application number: 93909715.0</p> <p>(22) Date of filing: 19.05.1993</p> | <p>(51) Int. Cl.⁶: A61L 29/00, C23C 14/14, B22F 9/04, C22F 1/00, C22C 45/00</p> <p>(86) International application number:
 PCT/CA93/00201</p> <p>(87) International publication number:
 WO 93/23092 (25.11.1993 Gazette 1993/28)</p> |
|---|---|

(54) **ANTI-MICROBIAL COATING FOR MEDICAL DEVICES**

ANTIMIKROBIELLE BESCHICHTUNG FÜR MEDIZINISCHE VORRICHTUNG
REKETEMENT ANTIMIKROBIEN DESTINE A DES INSTRUMENTS MEDICAUX

- | | |
|--|---|
| <p>(84) Designated Contracting States:
 AT BE CH DE DK ES FR GB IE IT LI NL PT SE</p> <p>(30) Priority: 19.05.1992 US 885758
 07.05.1993 US 57968</p> <p>(43) Date of publication of application:
 08.03.1995 Bulletin 1995/10</p> <p>(73) Proprietor:
 WESTAIM TECHNOLOGIES INC.
 Alberta T8L 3W4 (CA)</p> <p>(72) Inventors:
 <ul style="list-style-type: none"> • BURRELL, Robert, Edward
 Sherwood Park, Alberta T8A 4L6 (CA) • MORRIS, Larry, R.
 Edmonton, Alberta T6G 0T9 (CA) </p> | <p>(74) Representative: Gold, Tibor Z.
 Stephenson Harwood
 One, St. Paul's Churchyard
 London EC4M 8SH (GB)</p> <p>(56) References cited:
 EP-A- 0 415 206 GB-A- 2 073 024</p> <ul style="list-style-type: none"> • JOM vol. 41, no. 6, June 1989, WARRENDALE US pages 12 - 17 FROES ET AL. 'Nanocrystalline metals for structural applications' See pages 12-13, section "Synthesis"; Table I • TECHNISCHE MITTEILUNGEN KRUPP no. 2, November 1989, ESSEN DE pages 69 - 76 SCHLUMP ET AL 'Nanocrystalline materials by mechanical alloying' See whole document |
|--|---|

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 641 224 B1

Description

FIELD OF THE INVENTION

5 This invention relates to methods for preparing modified materials such as metal coatings or powders in a form such that metal species are released on a sustainable basis at an enhanced rate. In a particular aspect, the invention relates to methods of forming anti-microbial coatings and powders of biocompatible metals which provide a sustained release of anti-microbial metal species when in contact with body fluids or body tissues.

10 BACKGROUND OF THE INVENTION

The need for an effective anti-microbial coating is well established in the medical community. Physicians and surgeons using medical devices and appliances ranging from orthopaedic pins, plates and implants through to wound dressings and urinary catheters must constantly guard against infection. An inexpensive antimicrobial coating also finds
15 application in medical devices used in consumer healthcare and personal hygiene products as well as in biomedical/biotechnical laboratory equipment. The term "medical device", as used herein and in the claims is meant to extend to all such products.

The anti-microbial effects of metallic ions such as Ag, Au, Pt, Pd, Ir (i.e. the noble metals), Cu, Sn, Sb, Bi and Zn are known (see Morton, H.E., *Pseudomonas* in Disinfection, Sterilization and Preservation, ed. S.S. Block, Lea and Febiger, 1977 and Grier, N., *Silver and Its Compounds* in Disinfection, Sterilization and Preservation, ed. S.S. Block, Lea and Febiger, 1977). Of the metallic ions with anti-microbial properties, silver is perhaps the best known due to its
20 unusually good bioactivity at low concentrations. This phenomena is termed oligodynamic action. In modern medical practice both inorganic and organic soluble salts of silver are used to prevent and treat microbial infections. While these compounds are effective as soluble salts, they do not provide prolonged protection due to loss through removal or complexation of the free silver ions. They must be reapplied at frequent intervals to overcome this problem. Reapplication is not always practical, especially where an indwelling or implanted medical device is involved.

Attempts have been made to slow the release of silver ions during treatment by creating silver containing complexes which have a lower level of solubility. For example, U.S. Patent 2,785,153 discloses colloidal silver protein for this purpose. Such compounds are usually formulated as creams. These compounds have not found wide applicability in
30 the medical area due to their limited efficacy. The silver ion release rate is very slow. Furthermore, coatings from such compounds have been limited due to adhesion, abrasion resistance and shelf life problems.

The use of silver metal coatings for anti-microbial purposes has been suggested. For instance, see Deitch et al., *Antimicrobial Agents and Chemotherapy*, Vol. 23(3), 1983, pp. 356 - 359 and Mackeen et al., *Antimicrobial Agents and Chemotherapy*, Vol. 31(1), 1987, pp. 93 - 99. However, it is generally accepted that such coatings alone do not provide
35 the required level of efficacy, since diffusion of silver ions from the metallic surface is negligible.

A silver metal coating is produced by Spire Corporation, U.S.A. under the trade mark SPI-ARGENT. The coating is formed by an ion-beam assisted deposition (IBAD) coating process. The infection resistant coating is stated to be non-leaching in aqueous solutions as demonstrated by one of inhibition tests, thus enforcing the belief that silver metal surfaces do not release anti-microbial amounts of silver ions.

Given the failure of metallic silver coatings to generate the required anti-microbial efficacy, other researchers have tried novel activation processes. One technique is to use electrical activation of metallic silver implants (see Marino et al., *Journal of Biological Physics*, Vol. 12, 1984, pp. 93 - 98). Electrical stimulation of metallic silver is not always practical, especially for mobile patients. Attempts to overcome this problem include developing in situ electrical currents through galvanic action. Metal bands or layers of different metals are deposited on a device as thin film coatings. A galvanic cell is created when two metals in contact with each other are placed in an electrically conducting fluid. One metal
45 layer acts as an anode, which dissolves into the electrolyte. The second metal acts as a cathode to drive the electrochemical cell. For example, in the case of alternating layers of Cu and Ag, the Cu is the anode, releasing Cu^+ ions into the electrolyte. The more noble of the metals, Ag, acts as the cathode, which does not ionize and does not go into solution to any large extent. An exemplary device of this nature is described in U.S. Patent 4,886,505 issued Dec. 12, 1989, to Haynes et al. The patent discloses sputtered coatings of two or more different metals with a switch affixed to one of the metals such that, when the switch is closed, metal ion release is achieved.

Previous work has shown that a film composed of thin laminates of alternating, different metals such as silver and copper can be made to dissolve if the surface is first etched. In this instance, the etching process creates a highly textured surface (see M. Tanemura and F. Okuyama, *J. Vac. Sci. Technol.*, 5, 1986, pp 2369-2372). However, the process
55 of making such multilaminated films is time consuming and expensive.

Electrical activation of metallic coatings has not presented a suitable solution to the problem. It should be noted that galvanic action will occur only when an electrolyte is present and if an electrical connection between the two metals of the galvanic couple exists. Since galvanic corrosion occurs primarily at the metallic interface between the two metals,

electrical contact is not sustained. Thus a continuous release of metal ions over an extended period of time is not probable. Also, galvanic action to release a metal such as silver is difficult to achieve. As indicated above, the metal ions exhibiting the greatest anti-microbial effect are the noble metals, such as Ag, Au, Pt and Pd. There are few metals more noble than these to serve as cathode materials so as to drive the release of a noble metal such as Ag at the anode.

A second approach to activating the silver metal surface is to use heat or chemicals. U.S. Patents 4,476,590 and 4,615,705, issued to Scales et al. on October 16, 1984 and October 7, 1986, respectively, disclose methods of activating silver surface coatings on endoprosthetic implants to render them bioerodible by heating at greater than 180°C or by contacting with hydrogen peroxide. Such treatments are limited in terms of the substrate/devices which can be coated and activated.

There is still a need for an efficacious, inexpensive anti-microbial material having the following properties:

- sustained release of an anti-microbial agent at therapeutically active levels;
- applicable to a wide variety of devices and materials;
- useful shelf life; and
- low mammalian toxicity.

Metal coatings are typically produced as thin films by vapour deposition techniques such as sputtering. Thin films of metals, alloys, semiconductors and ceramics are widely used in the production of electronic components. These and other end uses require the thin films to be produced as dense, crystalline structures with minimal defects. The films are often annealed after deposition to enhance grain growth and recrystallization and produce stable properties. Techniques to deposit metal films are reviewed by R.F. Bunshah et al., "Deposition Technologies for Films and Coatings", Noyes Publications, N.J., 1982 and by J.A. Thornton, "Influence of Apparatus Geometry and Deposition Conditions on the Structure and Topography of Thick Sputtered Coatings", J. Vac. Sci. Technol., 11(4), 666-670, 1974.

U.S. Patent No. 4,325,776, issued April 20, 1982 to Menzel discloses a process for producing coarse or single crystal metal films from certain metals for use in integrated circuits. The metal film is formed by depositing on a cooled substrate (below -90°C) such that the metal layer is in an amorphous phase. The metal layer is then annealed by heating the substrate up to about room temperature. The end product is stated to have large grain diameter and great homogeneity, permitting higher current densities without electromigration failures.

SUMMARY OF THE INVENTION

The inventors set out to develop an antimicrobial metal coating. They discovered that, contrary to previous belief, it is possible to form metal coatings from an antimicrobial metal material by creating atomic disorder in the materials by vapour deposition under conditions which limit diffusion, that is which "freeze-in" the atomic disorder. The anti-microbial coatings so produced were found to provide sustained release of anti-microbial metal species into solution so as to produce an anti-microbial effect.

This basic discovery linking "atomic disorder" to enhanced solubility has broad application. The inventors have demonstrated that atomic disorder so as to produce solubility can be created in other material forms, such as metal powders. The invention also has application beyond antimicrobial metals, encompassing any metal, metal alloy, or metal compound, including semiconductor or ceramic materials, from which sustained release of metal species into solution is desired. For instance, materials having enhanced or controlled metal dissolution find application in sensors, switches, fuses, electrodes, and batteries.

The term "atomic disorder" as used herein includes high concentrations of: point defects in a crystal lattice, vacancies, line defects such as dislocations, interstitial atoms, amorphous regions, grain and sub grain boundaries and the like relative to its normal ordered crystalline state. Atomic disorder leads to irregularities in surface topography and inhomogeneities in the structure on a nanometre scale.

By the term "normal ordered crystalline state" as used herein is meant the crystallinity normally found in bulk metal materials, alloys or compounds formed as cast, wrought or plated metal products. Such materials contain only low concentrations of such atomic defects as vacancies, grain boundaries and dislocations.

The term "diffusion" as used herein implies diffusion of atoms and/or molecules on the surface or in the matrix of the material being formed.

The terms "metal" or "metals" as used herein are meant to include one or more metals whether in the form of substantially pure metals, alloys or compounds such as oxides, nitrides, borides, sulphides, halides or hydrides.

The invention, in a broad aspect extends to a method of forming a modified material containing one or more metals.

The method comprises creating atomic disorder in the material under conditions which limit diffusion such that sufficient atomic disorder is retained in the material to provide release, preferably on a sustainable basis, of atoms, ions, molecules or clusters of at least one of the metals into a solvent for the material. Clusters are known to be small groups of atoms, ions or the like, as described by R.P. Andres et al., "Research Opportunities on Clusters and Cluster-Assembled

Materials", J. Mater. Res. Vol. 4, No. 3, 1989, P. 704.

Specific preferred embodiments of the invention demonstrate that atomic disorder may be created in metal powders or foils by cold working, and in metal coatings by depositing by vapour deposition at low substrate temperatures.

In another broad aspect, the invention provides a modified material comprising one or more metals in a form characterized by sufficient atomic disorder such that the material, in contact with a solvent for the material, releases atoms, ions, molecules or clusters containing at least one metal, preferably on a sustainable basis, at an enhanced rate relative to its normal ordered crystalline state.

In preferred embodiments of the invention, the modified material is a metal powder which has been mechanically worked or compressed, under cold working conditions, to create and retain atomic disorder.

The term "metal powder" as used herein is meant to include metal particles of a broad particle size, ranging from nanocrystalline powders to flakes.

The term "cold working" as used herein indicates that the material has been mechanically worked such as by milling, grinding, hammering, mortar and pestle or compressing, at temperatures lower than the recrystallization temperature of the material. This ensures that atomic disorder imparted through working is retained in the material.

In another preferred embodiment, the modified material is a metal coating formed on a substrate by vapour deposition techniques such as vacuum evaporation, sputtering, magnetron sputtering or ion plating. The material is formed under conditions which limit diffusion during deposition and which limit annealing or recrystallization following deposition. The deposition conditions preferably used to produce atomic disorder in the coatings are outside the normal range of operating conditions used to produce defect free, dense, smooth films. Such normal practices are well known (see for example R.F. Bunshah et al., *supra*). Preferably the deposition is conducted at low substrate temperatures such that the ratio of the substrate to the melting point of the metal or metal compound being deposited (T/T_m) is maintained at less than about 0.5, more preferably at less than about 0.35, and most preferably at less than 0.30. In this ratio, the temperatures are in degrees Kelvin. The preferred ratio will vary from metal to metal and increases with alloy or impurity content. Other preferred deposition conditions to create atomic disorder include one or more of a higher than normal working gas pressure, a lower than normal angle of incidence of the coating flux and a higher than normal coating flux.

The temperature of deposition or cold working is not so low that substantial annealing or recrystallization will take place when the material is brought to room temperature or its intended temperature for use (ex. body temperature for antimicrobial materials). If the temperature differential between deposition and temperature of use (ΔT) is too great, annealing results, removing atomic disorder. This ΔT will vary from metal to metal and with the deposition technique used. For example, with respect to silver, substrate temperatures of -20 to 200°C are preferred during physical vapour deposition.

Normal or ambient working gas pressure for depositing the usually required dense, smooth, defect free metal films vary according to the method of physical vapour deposition being used. In general, for sputtering, the normal working gas pressure is less than 10 Pa (Pascal) (75 mT (milliTorr)), for magnetron sputtering, less than 1.0 Pa (10 mT), and for ion-plating less than 30 Pa (200 mT). Normal ambient gas pressures vary for vacuum evaporation processes vary as follows: for e-beam or arc evaporation, from 0.0001 Pa (0.001 mT) to 0.001 Pa (0.01 mT); for gas scattering evaporation (pressure plating) and reactive arc evaporation, up to 30 Pa (200 mT), but typically less than 3 Pa (20 mT). Thus, in accordance with the method of the present invention, in addition to using low substrate temperatures to achieve atomic disorder, working (or ambient) gas pressures higher than these normal values may be used to increase the level of atomic disorder in the coating.

Another condition discovered to have an effect on the level of atomic disorder in the coatings of the present invention is the angle of incidence of the coating flux during deposition. Normally to achieve dense, smooth coatings, this angle is maintained at about 90° +/- 15°. In accordance with the present invention, in addition to using low substrate temperatures during deposition to achieve atomic disorder, angles of incidence lower than about 75° may be used to increase the level of atomic disorder in the coating.

Yet another process parameter having an effect on the level of atomic disorder is the atom flux to the surface being coated. High deposition rates tend to increase atomic disorder, however, high deposition rates also tend to increase the coating temperature. Thus, there is an optimum deposition rate that depends on the deposition technique, the coating material and other process parameters.

To provide an anti-microbial material, the metals used in the coating or powder are those which have an antimicrobial effect, but which are biocompatible (non-toxic for the intended utility). Preferred metals include Ag, Au, Pt, Pd, Ir (i.e. the noble metals), Sn, Cu, Sb, Bi, and Zn, compounds of these metals or alloys containing one more of these metals. Such metals are hereinafter referred to as "anti-microbial metals". Most preferred is Ag or its alloys and compounds. Antimicrobial materials in accordance with this invention preferably are formed with sufficient atomic disorder that atoms, ions, molecules or clusters of the anti-microbial material are released into an alcohol or water based electrolyte on a sustainable basis. The terms "sustainable basis" is used herein to differentiate, on the one hand from the release obtained from bulk metals, which release metal ions and the like at a rate and concentration which is too low to achieve an anti-microbial effect, and on the other hand from the release obtained from highly soluble salts such as silver nitrate,

which release silver ions virtually instantly in contact with an alcohol or water based electrolyte. In contrast, the anti-microbial materials of the present invention release atoms, ions, molecules or clusters of the anti-microbial metal at a sufficient rate and concentration, over a sufficient time period to provide a useful anti-microbial effect.

The term "anti-microbial effect" as used herein means that atoms, ions, molecules or clusters of the anti-microbial metal are released into the electrolyte which the material contacts in concentrations sufficient to inhibit bacterial growth in the vicinity of the material. The most common method of measuring anti-microbial effect is by measuring the zone of inhibition (ZOI) created when the material is placed on a bacterial lawn. A relatively small or no ZOI (ex. less than 1 mm) indicates a non-useful anti-microbial effect, while a larger ZOI (ex. greater than 5 mm) indicates a highly useful anti-microbial effect. One procedure for a ZOI test is set out in the Examples which follow.

The invention extends to devices such as medical devices formed from, incorporating, carrying or coated with the anti-microbial powders or coatings. The anti-microbial coating may be directly deposited by vapour deposition onto such medical devices as catheters, sutures, implants, bum dressings and the like. An adhesion layer, such as tantalum, may be applied between the device and the anti-microbial coating. Adhesion may also be enhanced by methods known in the art, for example etching the substrate or forming a mixed interface between the substrate and the coating by simultaneous sputtering and etching. Anti-microbial powders may be incorporated into creams, polymers, ceramics, paints, or other matrices, by techniques well known in the art.

In a further broad aspect of the invention, modified materials are prepared as composite metal coatings containing atomic disorder. In this case, the coating of the one or more metals or compounds to be released into solution constitutes a matrix containing atoms or molecules of a different material. The presence of different atoms or molecules results in atomic disorder in the metal matrix, for instance due to different sized atoms. The different atoms or molecules may be one or more second metals, metal alloys or metal compounds which are co- or sequentially deposited with the first metal or metals to be released. Alternatively the different atoms or molecules may be absorbed or trapped from the working gas atmosphere during reactive vapour deposition. The degree of atomic disorder, and thus solubility, achieved by the inclusion of the different atoms or molecules varies, depending on the materials. In order to retain and enhance the atomic disorder in the composite material, one or more of the above-described vapour deposition conditions, namely low substrate temperature, high working gas pressure, low angle of incidence and high coating flux, may be used in combination with the inclusion of different atoms or molecules.

Preferred composite materials for anti-microbial purposes are formed by including atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur or halogens in the working gas atmosphere while depositing the anti-microbial metal. These atoms or molecules are incorporated in the coating either by being absorbed or trapped in the film, or by reacting with the metal being deposited. Both of these mechanisms during deposition are hereinafter referred to as "reactive deposition". Gases containing these elements, for example oxygen, hydrogen, and water vapour, may be provided continuously or may be pulsed for sequential deposition.

Anti-microbial composite materials are also preferably prepared by co- or sequentially depositing an anti-microbial metal with one or more inert biocompatible metals selected from Ta, Ti, Nb, Zn, V, Hf, Mo, Si, and Al. Alternatively, the composite materials may be formed by co-, sequentially or reactively depositing one or more of the anti-microbial metals as the oxides, carbides, nitrides, borides, sulphides or halides of these metals and/or the oxides, carbides, nitrides, borides, sulphides or halides of the inert metals. Particularly preferred composites contain oxides of silver and/or gold, alone or together with one or more oxides of Ta, Ti, Zn and Nb.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As above stated, the present invention has application beyond anti-microbial materials. However, the invention is disclosed herein with anti-microbial metals, which are illustrative of utility for other metals, metal alloys and metal compounds. Preferred metals include Al and Si, and the metal elements from the following groups of the periodic table: IIIB, IVB, VB, VIB, VIIB, VIIIB, IB, IIB, IIIA, IVA, and VA (excluding As) in the periods 4, 5 and 6, (see Periodic Table as published in Merck Index 10th Ed., 1983, Merck and Co. Inc., Rahway, N.J., Martha Windholz). Different metals will have varying degrees of solubility. However, the creation and retention of atomic disorder in accordance with this invention results in enhanced solubility (release) of the metal as ions, atoms, molecules or clusters into an appropriate solvent i.e. a solvent for the particular material, typically a polar solvent, over the solubility of the material in its normal ordered crystalline state.

The medical devices formed from, incorporating, carrying or coated with the anti-microbial material of this invention generally come into contact with an alcohol or water based electrolyte including a body fluid (for example blood, urine or saliva) or body tissue (for example skin, muscle or bone) for any period of time such that microorganism growth on the device surface is possible. The term "alcohol or water based electrolyte" also includes alcohol or water based gels. In most cases the devices are medical devices such as catheters, implants, tracheal tubes, orthopaedic pins, insulin pumps, wound closures, drains, dressings, shunts, connectors, prosthetic devices, pacemaker leads, needles, surgical instruments, dental prostheses, ventilator tubes and the like. However, it should be understood that the invention is not

limited to such devices and may extend to other devices useful in consumer healthcare, such as sterile packaging, clothing and footwear, personal hygiene products such as diapers and sanitary pads, in biomedical or biotechnical laboratory equipment, such as tables, enclosures and wall coverings, and the like. The term "medical device" as used herein and in the claims is intended to extend broadly to all such devices.

The device may be made of any suitable material, for example metals, including steel, aluminum and its alloys, latex, nylon, silicone, polyester, glass, ceramic, paper, cloth and other plastics and rubbers. For use as an in-dwelling medical device, the device will be made of a bioinert material. The device may take on any shape dictated by its utility, ranging from flat sheets to discs, rods and hollow tubes. The device may be rigid or flexible, a factor again dictated by its intended use.

Anti-Microbial Coatings

The anti-microbial coating in accordance with this invention is deposited as a thin metallic film on one or more surfaces of a medical device by vapour deposition techniques. Physical vapour techniques, which are well known in the art, all deposit the metal from the vapour, generally atom by atom, onto a substrate surface. The techniques include vacuum or arc evaporation, sputtering, magnetron sputtering and ion plating. The deposition is conducted in a manner to create atomic disorder in the coating as defined hereinabove. Various conditions responsible for producing atomic disorder are useful. These conditions are generally avoided in thin film deposition techniques where the object is to create a defect free, smooth and dense film (see for example J.A. Thornton, *supra*). While such conditions have been investigated in the art, they have not heretofore been linked to enhanced solubility of the coatings so-produced.

The preferred conditions which are used to create atomic disorder during the deposition process include:

- a low substrate temperature, that is maintaining the surface to be coated at a temperature such that the ratio of the substrate temperature to the melting point of the metal (in degrees Kelvin) is less than about 0.5, more preferably less than about 0.35 and most preferably less than about 0.3; and optionally one or both of:
- a higher than normal working (or ambient) gas pressure, i.e. for vacuum evaporation: e-beam or arc evaporation, greater than 0.001 Pa (0.01 mT), gas scattering evaporation (pressure plating) or reactive arc evaporation, greater than 3 Pa (20 mT); for sputtering: greater than 10 Pa (75 mT); for magnetron sputtering: greater than about 1 Pa (10 mT); and for ion plating: greater than about 30 Pa (200 mT); and
- maintaining the angle of incidence of the coating flux on the surface to be coated at less than about 75°, and preferably less than about 30°

The metals used in the coating are those known to have an antimicrobial effect. For most medical devices, the metal must also be biocompatible. Preferred metals include the noble metals Ag, Au, Pt, Pd, and Ir as well as Sn, Cu, Sb, Bi, and Zn or alloys or compounds of these metals or other metals. Most preferred is Ag or Au, or alloys or compounds of one or more of these metals.

The coating is formed as a thin film on at least a part of the surface of the medical device. The film has a thickness no greater than that needed to provide release of metal ions on a sustainable basis over a suitable period of time. In that respect, the thickness will vary with the particular metal in the coating (which varies the solubility and abrasion resistance), and with the degree of atomic disorder in (and thus the solubility of) the coating. The thickness will be thin enough that the coating does not interfere with the dimensional tolerances or flexibility of the device for its intended utility. Typically, thicknesses of less than 1 micron have been found to provide sufficient sustained anti-microbial activity. Increased thicknesses may be used depending on the degree of metal ion release needed over a period of time. Thicknesses greater than 10 microns are more expensive to produce and normally should not be needed.

The anti-microbial effect of the coating is achieved when the device is brought into contact with an alcohol or a water based electrolyte such as, a body fluid or body tissue, thus releasing metal ions, atoms, molecules or clusters. The concentration of the metal which is needed to produce an antimicrobial effect will vary from metal to metal. Generally, anti-microbial effect is achieved in body fluids such as plasma, serum or urine at concentrations less than about 0.5 - 1.5 µg/ml.

The ability to achieve release of metal atoms, ions, molecules or clusters on a sustainable basis from a coating is dictated by a number of factors, including coating characteristics such as composition, structure, solubility and thickness, and the nature of the environment in which the device is used. As the level of atomic disorder is increased, the amount of metal ions released per unit time increases. For instance, a silver metal film deposited by magnetron sputtering at $T/T_m < 0.5$ and a working gas pressure of about 0.9 Pa (7 mTorr) releases approximately 1/3 of the silver ions that a film deposited under similar conditions, but at 4 Pa (30 mTorr), will release over 10 days. Films that are created with an intermediate structure (ex. lower pressure, lower angle of incidence etc.) have Ag release values intermediate to these values as determined by bioassays. This then provides a method for producing controlled release metallic coatings in accordance with this invention. Slow release coatings are prepared such that the degree of disorder is low while

fast release coatings are prepared such that the degree of disorder is high.

For continuous, uniform coatings, the time required for total dissolution will be a function of film thickness and the nature of the environment to which they are exposed. The relationship in respect of thickness is approximately linear, i.e. a two fold increase in film thickness will result in about a two fold increase in longevity.

It is also possible to control the metal release from a coating by forming a thin film coating with a modulated structure. For instance, a coating deposited by magnetron sputtering such, that the working gas pressure was low (ex. 2 Pa (15 mTorr)) for 50% of the deposition time and high (ex. 4 Pa (30 mTorr)) for the remaining time, has a rapid initial release of metal ions, followed by a longer period of slow release. This type of coating is extremely effective on devices such as urinary catheters for which an initial rapid release is required to achieve immediate antimicrobial concentrations followed by a lower release rate to sustain the concentration of metal ions over a period of weeks.

The substrate temperature used during vapour deposition should not be so low that annealing or recrystallization of the coating takes place as the coating warms to ambient temperatures or the temperatures at which it is to be used (ex. body temperature). This allowable ΔT , that the temperature differential between the substrate temperature during deposition and the ultimate temperature of use, will vary from metal to metal. For the most preferred metals of Ag and Au, preferred substrate temperatures of -20 to 200°C, more preferably -10°C to 100°C are used.

Atomic order may also be achieved, in accordance with the present invention, by preparing composite metal materials, that is materials which contain one or more anti-microbial metals in a metal matrix which includes atoms or molecules different from the anti-microbial metals.

Our technique for preparing composite material is to co- or sequentially deposit the anti-microbial metal(s) with one or more other inert, biocompatible metals selected from Ta, Ti, Nb, Zn, V, Hf, Mo, Si, Al and alloys of these metals or other metal elements, typically other transition metals. Such inert metals have a different atomic radii from that of the anti-microbial metals, which results in atomic disorder during deposition. Alloys of this kind can also serve to reduce atomic diffusion and thus stabilize the disordered structure. Thin film deposition equipment with multiple targets for the placement of each of the anti-microbial and inert metals is preferably utilized. When layers are sequentially deposited the layer(s) of the inert metal(s) should be discontinuous, for example as islands within the anti-microbial metal matrix. The final ratio of the anti-microbial metal(s) to inert metal(s) should be greater than about 0.2. The most preferable inert metals are Ti, Ta, Zn and Nb. It is also possible to form the anti-microbial coating from oxides, carbides, nitrides, sulphides, borides, halides or hydrides of one or more of the anti-microbial metals and/or one or more of the inert metals to achieve the desired atomic disorder.

Another composite material within the scope of the present invention is formed by reactively co- or sequentially depositing, by physical vapour techniques, a reacted material into the thin film of the antimicrobial metal(s). The reacted material is an oxide, nitride, carbide, boride, sulphide, hydride or halide of the anti-microbial and/or inert metal, formed in situ by injecting the appropriate reactants, or gases containing same, (ex. air, oxygen, water, nitrogen, hydrogen, boron, sulphur, halogens) into the deposition chamber. Atoms or molecules of these gases may also become absorbed or trapped in the metal film to create atomic disorder. The reactant may be continuously supplied during deposition for codeposition or it may be pulsed to provide for sequential deposition. The final ratio of anti-microbial metal(s) to reaction product should be greater than about 0.2. Air, oxygen, nitrogen and hydrogen are particularly preferred reactants.

The above deposition techniques to prepare composite coatings may be used with or without the conditions of lower substrate temperatures, high working gas pressures and low angles of incidence previously discussed. One or more of these conditions is preferred to retain and enhance the amount of atomic disorder created in the coating.

It may be advantageous, prior to depositing an anti-microbial in accordance with the present invention, to provide an adhesion layer on the device to be coated, as is known in the art. For instance, for a latex device, a layer of Ti, Ta or Nb may be first deposited to enhance adhesion of the subsequently deposited anti-microbial coating.

Anti-Microbial Powders

Anti-microbial powders, including nanocrystalline powders and powders made from rapidly solidified flakes or foils, can be formed with atomic disorder so as to enhance solubility. The powders either as pure metals, metal alloys or compounds such as metal oxides or metal salts, can be mechanically worked or compressed to impart atomic disorder. This mechanically imparted disorder is conducted under conditions of low temperature (i.e. temperatures less than the temperature of recrystallization of the material) to ensure that annealing or recrystallization does not take place. The temperature varies between metals and increases with alloy or impurity content.

Anti-microbial powders produced in accordance with this invention may be used in a variety of forms, for instance in topical creams, paints or adherent coatings. Alternatively, the powder may be incorporated into a polymeric, ceramic or metallic matrix to be used as a material for medical devices or coatings therefor.

The invention is further illustrated by the following non-limiting examples.

Example 1

A medical suture material size 2/0, polyester braid was coated by magnetron sputtering an Ag-Cu-alloy onto the surface to a thickness of 0.45 microns, using either argon gas working pressures of 0.9 Pa (7 mTorr) or 4 Pa (30 mT) at 0.5 KW power and a T/Tm ratio of less than 0.5.

The anti-microbial effect of the coatings was tested by a zone of inhibition test. Basal medium Eagle (BME) with Earle's salts and L-glutamine was modified with calf/serum (10%) and 1.5 % agar prior to being dispensed (15 ml) into Petri dishes. The agar containing Petri plates were allowed to surface dry prior to being inoculated with a lawn of *Staphylococcus aureus* ATCC# 25923. The inoculant was prepared from Bactrol Discs (Difco, M.) which were reconstituted as per the manufacturer's directions. Immediately after inoculation, the materials or coatings to be tested were placed on the surface of the agar. The dishes were incubated for 24 h at 37°C. After this incubation period, the zone of inhibition was measured and a corrected zone of inhibition was calculated (corrected zone of inhibition = zone of inhibition - diameter of the test material in contact with the agar).

The results showed no zone of inhibition on the uncoated suture, a zone of less than 0.5 mm around the suture coated at 0.9 Pa (7 mTorr) and a zone of 13 mm around the suture coated at 4 Pa (30 mTorr). Clearly the suture coated in accordance with the present invention exhibits a much more pronounced and effective antimicrobial effect.

Example 2

This example is included to illustrate the surface structures which are obtained when silver metal is deposited on silicon wafers using a magnetron sputtering facility and different working gas pressures and angles of incidence (i.e. the angle between the path of the sputtered atoms and the substrate). All other conditions were as follows: deposition rate was 200 Å/min; ratio of temperature of substrate (wafer) to melting point of silver (1234°K), T/Tm was less than 0.3. Argon gas pressures of 0.9 Pa (7 mTorr) (a normal working pressure for metal coatings) and 4 Pa (30 mTorr) were used. Angles of incidence at each of these pressures were 90° (normal incidence), 50° and 10°. The coatings had a thickness of about 0.5 microns.

The resulting surfaces were viewed by scanning electron microscope. As argon gas pressure increased from 0.9 Pa (7 mTorr) to 4 Pa (30 mTorr) the grain size decreased and void volume increased significantly. When the angle of incidence was decreased, the grain size decreased and the grain boundaries became more distinct. At 0.9 Pa (7 mTorr) argon pressure and an angle of incidence of 10°, there were indications of some voids between the grains. The angle of incidence had a greater effect on the surface topography when the gas pressure was increased to 4 Pa (30 mTorr). At 90°, the grain size varied from 60 - 150 nm and many of the grains were separated by intergrain void spaces which were 15 - 30 nm wide. When the angle of incidence was decreased to 50°, the grain size decreased to 30 - 90 nm and the void volume increased substantially. At 10°, the grain size was reduced to about 10 - 60 nm and void volumes were increased again.

The observed nanometre scale changes in surface morphology and topography are indications of atomic disorder in the silver metal. While not being bound by the same, it is believed that such atomic disorder results in an increase in the chemical activity due to increased internal stresses and surface roughness created by mismatched atoms. It is believed that the increased chemical activity is responsible for the increased level of solubility of the coatings when in contact with an electrolyte such as body fluid.

The anti-microbial effect of the coatings was evaluated using the zone of inhibition test as set out in Example 1. Each coated silicon wafer was placed on an individual plate. The results were compared to the zones of inhibition achieved when solid silver (i.e. greater than 99% silver) sheets, wires or membranes were tested. The results are summarized in Table 1. It is evident that the pure silver devices and the silver sputtered coating at 0.9 Pa (7 mTorr) do not produce any biological effect. However, the coatings deposited at a higher than normal working-gas pressure, 4 Pa (30 mTorr), demonstrated an anti-microbial effect, as denoted by the substantial zones of inhibition around the discs. Decreasing the angle of incidence had the greatest effect on anti-microbial activity when combined with the higher gas pressures.

Table I

Antimicrobial effects of various silver and silver coated samples as determined using <i>Staphylococcus aureus</i>				
Sample	Percent Silver	Angle of Deposition	Working Gas Pressure Pa (mTorr)	Corrected Zone of Inhibition (mm)
Silver Sheet-rolled	99+	-	-	<0.5
Silver wire (.0045")	99+	-	-	<0.5

Table I (continued)

Antimicrobial effects of various silver and silver coated samples as determined using <i>Staphylococcus aureus</i>				
Sample	Percent Silver	Angle of Deposition	Working Gas Pressure Pa (mTorr)	Corrected Zone of Inhibition (mm)
Silver membrane cast	99+	-	-	<0.5
Sputtered thin film	99+	normal (90°)	0.9 (7)	<0.5
Sputtered thin film	99+	50°	0.9 (7)	<0.5
Sputtered thin film	99+	10°	0.9 (7)	<0.5
Sputtered thin film	99+	normal (90°)	4 (30)	6.3
Sputtered thin film	99+	50°	4 (30)	10
Sputtered thin film	99+	10	4 (30)	10

Example 3

Silicon wafers were coated by magnetron sputtering with an alloy of Ag and Cu (80:20) at normal incidence at working gas pressures of 0.9 Pa (7 mTorr) and 4 Pa (30 mTorr), all other conditions being identical to those set out in Example 2. As in Example 2, when the coatings were viewed by SEM, the coatings formed at high working gas pressure had smaller grain sizes and larger void volumes than did the coatings formed at the lower working gas pressures.

Coatings which were similarly formed from a 50:50 Ag/Cu alloy were tested for anti-microbial activity with the zone of inhibition test set out in Example 1. The results are summarized in Table 2. Coatings deposited at low working gas pressure (0.9 Pa (7 mTorr)) showed minimal zones of inhibition, while the coatings deposited at high working gas pressure (4 Pa (30 mTorr)) produced larger zones of inhibition, indicative of anti-microbial activity.

Table 2

The antimicrobial effect of various sputter deposited silver-copper alloys as determined using <i>Staphylococcus aureus</i>				
Sample	Percent Silver	Angle of Deposition (°)	Working Gas Pressure Pa (mTorr)	Corrected Zone of Inhibition (mm)
1	50	normal (90°)	1.0 (7.5)	<0.5
2	50	normal (90°)	4 (30)	16
3	50	10	4 (30)	19

Example 4

A coating in accordance with the present invention was tested to determine the concentration of silver ions released into solution over time. One cm² silicon wafer discs were coated with silver as set forth in Example 2 at 0.9 Pa (7 mTorr) and 4 Pa (30 mTorr) and normal incidence to a thickness of 5000 Å. Using the method of Nickel et al., Eur. J. Clin. Microbiol., 4(2), 213-218, 1985, a sterile synthetic urine was prepared and dispensed into test tubes (3.5 ml). The coated discs were placed into each test tubes and incubated for various times at 37°C. After various periods of time, the discs were removed and the Ag content of the filtered synthetic urine was determined using neutron activation analysis.

The results are set forth in Table 3. The table shows the comparative amounts of Ag released over time from coatings deposited on discs at 0.9 Pa (7 mTorr) or 4 Pa (30 mTorr). The coatings deposited at high pressure were more soluble than those deposited at low pressure. It should be noted that this test is a static test. Thus, silver levels build up over time, which would not be the case in body fluid where there is constant turn over.

Table 3

Concentration of silver in synthetic urine as a function of exposure time Silver Concentration $\mu\text{g/ml}$		
Exposure Time (Days)	Working Argon gas pressure 0.9 Pa (7 mTorr)	Working argon gas pressure 4 Pa (30 mTorr)
0	ND1	ND
1	0.89	1.94
3	1.89	2.36
10	8.14	23.06
Note: Films were deposited at normal incidence (90°) 1 - ND (non detectable) $<0.46 \mu\text{g/ml}$		

Example 5

This example is included to illustrate coatings in accordance with the present invention formed from another noble metal, Pd. The coatings were formed on silicon wafers as set forth in Example 2, to a thickness of 5000 Å, using 0.9 Pa (7 mTorr) or 4 Pa (30 mTorr) working gas pressures and angles of incidence of 90° and 10° . The coated discs were evaluated for antimicrobial activity by the zone of inhibition test substantially as set forth in Example 1. The coated discs were placed coating side up such that the agar formed a 1 mm surface coating over the discs. The medium was allowed to solidify and surface dry, after which the bacterial lawn was spread over the surface. The dishes were incubated at 37°C for 24 h. The amount of growth was then visually analyzed.

The results are set forth in Table 4. At high working gas pressures, the biological activity of the coating was much greater than that of coatings deposited at low pressure. Changing the angle of incidence (decreasing) improved the anti-microbial effect of the coating to a greater extent when the gas pressure was low than when it was high.

Table 4

Surface Control of <u>Staphylococcus aureus</u> by Sputter Deposited Palladium metal			
Sample	Sputtering Pressure Pa (mTorr)	Angle of Deposition	Antimicrobial Control
1	0.9 (7)	90° (normal incidence)	More than 90% of surface covered by bacterial growth
2	0.9 (7)	10° (grazing incidence)	20-40% of surface covered by bacterial growth
3	4 (30)	90° (normal incidence)	Less than 10% surface covered by bacterial growth

Example 6

This example is included to illustrate the effect of silver deposition temperature on the antimicrobial activity of the coating. Silver metal was deposited on 2.5 cm sections of a latex Foley catheter using a magnetron sputtering facility. Operating conditions were as follows; the deposition rate was 200 Å per minute; the argon working gas pressure was 4 Pa (30 mTorr); and the ratio of temperature of substrate to melting point of the coating metal silver, T/T_m was 0.30 or 0.38. In this example the angles of incidence were variable since the substrate was round and rough. That is the angles of incidence varied around the circumference and, on a finer scale, across the sides and tops of the numerous surface features. The antimicrobial effect was tested by a zone of inhibition test as outlined in Example 1.

The results showed corrected zones of inhibition of 0.5 and 16 mm around the tubing coated at T/T_m values of 0.38 and 0.30 respectively. The sections of Foley catheter coated at the lower T/T_m value were more efficacious than those coated at higher T/T_m value.

Example 7

This example is included to demonstrate an antimicrobial coating formed by DC magnetron sputtering on a commercial catheter. A teflon coated latex Foley catheter was coated by DC magnetron sputtering 99.99% pure silver on the surface using the conditions listed in Table 5. The working gases used were commercial Ar and 99/1 wt% Ar/O₂. The antimicrobial effect of the coating was tested by a zone of inhibition test. Mueller Hinton agar was dispensed into Petri dishes. The agar plates were allowed to surface dry prior to being inoculated with a lawn of *Staphylococcus aureus* ATCC# 25923. The inoculant was prepared from Bactrol Discs (Difco, M.) which were reconstituted as per the manufacturer's directions. Immediately after inoculation, the coated materials to be tested were placed on the surface of the agar. The dishes were incubated for 24 hr. at 37°C. After this incubation period, the zone of inhibition was measured and a corrected zone of inhibition was calculated (corrected zone of inhibition = zone of inhibition - diameter of the test material in contact with the agar).

The results showed no zone of inhibition for the uncoated samples and a corrected zone of less than 1 mm for catheters sputtered in commercial argon at a working gas pressure of 0.7 Pa (5 mT). A corrected zone of inhibition of 11 mm was reported for the catheters sputtered in the 99/1 wt% Ar/O₂ using a working gas pressure of 5.3 Pa (40 mT). XRD analysis showed that the coating sputtered in 1% oxygen was a crystalline Ag film. This structure clearly caused an improved anti-microbial effect for the coated catheters.

Table 5

Conditions of DC Magnetron Sputtering Used for Anti-Microbial Coatings	
Samples Sputtered in Commercial Argon	Samples Sputtered in 99/1 wt% Ar/O ₂
Power 0.1 kW	Power 0.5 kW
Argon Pressure: 0.7 Pa (5 mTorr)	Ar/O ₂ Pressure: 5.3 Pa (40 mTorr)
Initial Substrate Temperature: 20°C	Initial Substrate Temperature: 20°C
Cathode/Anode Distance: 40 mm	Cathode/Anode Distance: 100mm
Film Thickness: 2500 Å	Film Thickness: 3000 Å

Example 8

This example demonstrates silver coatings formed by arc evaporation, gas scattering evaporation (pressure plating) and reactive arc evaporation. Evaporation of 99.99% silver was performed onto silicon or alumina wafers at an initial substrate temperature of about 21°C, using the parameters as follows:

Bias: -100 V

Current: 20 Amp-hrs

Angle of incidence: 90°

Working Gas Pressure: 0.001 Pa (0.01 mT) (arc), 3.5 Pa (26 mT) Ar/H₂ 96:4 (gas scattering evaporation), and 3.5 Pa (26 mT) O₂ (reactive arc evaporation)

No corrected ZOI was observed for wafers coated at vacuum (arc). Pressure plating with a working gas atmosphere containing Ar and 4 % hydrogen produced a 6 mm ZOI, while a working gas atmosphere of pure oxygen (reactive arc) produced an 8 mm ZOI. Film thicknesses of about 4000 Angstroms were produced. The results indicate that the presence of gases such as hydrogen and/or oxygen in the arc evaporation atmosphere cause the coatings to have improved anti-microbial efficacy.

Example 9

This example is included to illustrate composite materials to produce anti-microbial effects. A set of coatings were produced by RF magnetron sputtering zinc oxide onto silicon wafers as outlined below. The zinc oxide coatings showed no zone of inhibition.

Coatings of Ag and ZnO were deposited to a total thickness of 3300 Angstroms by sequentially sputtering layers of

Ag with layers of ZnO, according to the conditions below, in a 75/25 wt% ratio. The coatings were demonstrated to have no zone of inhibition when the zinc oxide layers were about 100 Angstroms thick. However, films consisting of islands of very thin to discontinuous layers of ZnO (less than 50 Angstroms) in an Ag matrix (ie. a composite film) had a 8 mm corrected zone of inhibition.

The conditions used to deposit ZnO were as follows: Working gas = argon; Working gas pressure = 4 Pa (30 mT); Cathode-Anode distance: 40 mm; Initial Substrate Temperature: 21°C; Power: RF magnetron, 0.5 kW.

The conditions used to deposit the Ag were as follows: Working gas = argon; Working gas pressure = 4 Pa (30 mT); Cathode-Anode distance = 40 mm; Initial Substrate Temperature = 21°C; Power = DC magnetron, 0.1 kW.

Example 10

This example demonstrates the effects of cold working and annealing silver and gold powders on the antimicrobial efficacy demonstrated by a standard zone of inhibition test. Cold working of such powders results in a defective surface structure containing atomic disorder which favours the release of ions causing antimicrobial activity. The antimicrobial effect of this defective structure can be removed by annealing.

Nanocrystalline silver powder (crystal size about 30 nm) was sprinkled onto adhesive tape and tested. A zone of inhibition of 5 mm was obtained, using the method set forth in Example 7. A 0.3g pellet of the nanocrystalline Ag powder was pressed at 275,700 kPa (kiloPascal) (40,000 psi). The pellet produced a 9 mm zone of inhibition when tested for antimicrobial activity. Nanocrystalline silver powder was mechanically worked in a ball mill for 30 sec. The resulting powder was tested for antimicrobial activity, both by sprinkling the worked powder on adhesive tape and applying to the plates, and by pressing the powder into a pellet at the above conditions and placing the pellet on the plates. The zones of inhibition observed were 7 and 11 mm respectively. A pellet that had been pressed from the worked powder was annealed at 500°C for 1 hour under vacuum conditions. A reduced zone of inhibition of 3 mm was observed for the annealed pellet.

These results demonstrate that nanocrystalline silver powder, while having a small anti-microbial effect on its own, has an improved antimicrobial effect by introducing atomic disorder by mechanical working of the powder in a ball mill or by pressing it into a pellet. The antimicrobial effect was significantly decreased by annealing at 500°C. Thus, conditions of mechanical working should not include or be followed by conditions such as high temperature, which allow diffusion. Cold mechanical working conditions are preferred to limit diffusion, for example by working at room temperature or by grinding or milling in liquid nitrogen.

Silver powder, 1 micron particle size, was tested in a manner similar to above. The Ag powder sprinkled onto adhesive tape and tested for a zone of inhibition. No zone of inhibition was observed. The powder was worked in a ball mill for 30 seconds and sprinkled onto adhesive tape. A 6 mm zone of inhibition was observed around the powder on the tape. When the Ag powder (as is or after mechanical working in the ball mill) was pressed into a 0.3 g pellet using 275,700 kPa (40,000 psi), zones of inhibition of 5 and 6 mm respectively were observed. A pellet which was formed from the ball milled powder and which was annealed at 500°C for 1 hour had significantly reduced antimicrobial activity. Initially the pellet had some activity (4.5 mm zone of inhibition) but after the pellet was tested a second time, no zone of inhibition was observed. A control pellet which had not been annealed continued to give a zone of inhibition greater than 4 mm even after 14 repeats of the test. This demonstrates that an annealing step, following by mechanical working, limits the sustainable release of the antimicrobial silver species from the powders.

Nanocrystalline gold (20 nm crystals), supplied as a powder, was tested for anti-microbial effect by sprinkling the powder onto adhesive tape and using the zone of inhibition test. No zone of inhibition was recorded for the nanocrystalline gold powder. The gold powder was pressed into a 0.2 g pellet using 275,700 kPa (40,000 psi). A 10 mm zone of inhibition was observed. When the pressed pellets were subsequently vacuum annealed at 500°C for 1 hour and the zone of inhibition was found to be 0 mm.

The results showed that solubility and thus the anti-microbial efficacy of gold powders can be improved by a mechanical working process such as pressing a nanocrystalline material into a pellet. The antimicrobial activity can be removed by annealing. Cold working is preferred.

Other gold powders including a 2-5 micron and a 250 micron particle size powder did not demonstrate an antimicrobial effect under the above mechanical working conditions. It is believed that the small grain size of the nanocrystalline gold powder was an important cofactor which, with the mechanical working, produced the desired antimicrobial effect.

Example 11

This example is included to demonstrate a composite antimicrobial coating formed by reactive sputtering (another example of composite films). Example 7 demonstrates that an antimicrobial coating of silver can be obtained by sputtering in argon and 1 % oxygen (0.5 kW, 5.3 Pa (40 mTorr), 100 mm anode/cathode distance, and 20°C - produced a

zone of inhibition of 11 mm).

When a working gas of argon and 20 wt% oxygen was used to sputter antimicrobial coatings under the conditions listed below in Table 6, the zones of inhibition ranged from 6 to 12 mm. This indicates that the provision of a reactive atmosphere during vapour deposition has the result of producing an antimicrobial film over a wide range of deposition process parameters.

Table 6

Sputtering Conditions	
Target	99.99% Ag
Working Gas:	80/20 wt% Ar/O ₂
Working Gas Pressure:	0.3 to 6.7 Pa (2.5 to 50 mTorr)
Power:	0.1 to 2.5 kW
Substrate Temperature:	-5 to 20°C
Anode/Cathode Distance	40 to 100 mm
Base Pressure:	less than 5×10^{-4} Pa (4×10^{-6} Torr)

Example 12

This example demonstrates that the coatings of this invention have an antimicrobial effect against a broad spectrum of bacteria.

A total of 171 different bacterial samples encompassing 18 genera and 55 species were provided by the Provincial Laboratory of Public Health for Northern Alberta. These samples had been quick frozen in 20% skim milk and stored at -70°C for periods ranging from several months to several years. Fastidious organisms which were unlikely to grow under conditions used in standard Kirby-Bauer susceptibility testing were not used.

Each frozen sample was scraped with a sterile cotton swab to inoculate a blood agar plate (BAP). The plates were incubated overnight at 35°C. The following morning isolated colonies were subcultured onto fresh BAPs and incubated at 35°C overnight. The next day, the organisms were subjected to Kirby-Bauer susceptibility testing as described below.

Four to five colonies (more if colonies were small) of the same morphological type were selected from each BAP subculture and inoculated into individual tubes containing approximately 5 mL of tryptic soy broth (TSB). The broths were incubated at 35°C for approximately 2 to 3 hours. At this time, the turbidity of most of the broth cultures either equalled or exceeded that of a 0.5 McFarland standard. The more turbid samples were diluted with sterile saline to obtain a turbidity visually comparable to that of the standard. To aid in the visual assessment of turbidity, tubes were read against a white background with contrasting black line.

A small number of the organisms (*Streptococcus* and *Corynebacterium*) did not grow well in TSB. The turbidity of these broths, after incubation, was less than that of the 0.5 McFarland standard. Additional colonies from the BAP subcultures were inoculated to these tubes to increase the turbidity to approximate that of the standard.

Within 15 minutes of adjusting the turbidity of the bacterial suspensions a sterile cotton swab was dipped into each broth. Excess fluid was removed by rotating the swab against the rim of the tube. The inoculum was applied to a Mueller Hinton (MH) agar plate by streaking the swab evenly in three directions over the entire agar surface. Three 1 cm x 1 cm silver coated silica wafer squares were applied to each MH plate and the plates were inverted and incubated overnight at 35°C. The coatings had been sputtered under the following conditions, which through XFD analysis were shown to be silver/silver oxide composite films:

Target:	99.99% Ag
Working gas:	Ar/O ₂ 80/20
Working gas pressure:	5.3 Pa (40 mT)
Power:	0.1 kW
Temperature of Deposition	20°C

EP 0 641 224 B1

(continued)

Base pressure	2.7×10^{-4} Pa (2×10^{-6} Torr)
Cathode/anode distance	40 mm

BAP cultures of control organisms were provided by the Provincial Laboratory and included: *Staphylococcus aureus* ATCC 25923; *Pseudomonas aeruginosa* ATCC 27853; *Escherichia coli*: ATCC 25922; and *Enterococcus faecalis* ATCC 29212 to check the quality of the MH agar. These cultures were treated in a like manner to the test organisms except that standard antibiotic discs rather than silver coated wafers were applied to the bacterial lawns on the MH agar. These organisms demonstrated that the MH agar was suitable for standard ZOI tests.

After 16 to 18 hours of incubation at 35°C zones of inhibition around the silver wafers or antibiotic discs were measured to the nearest mm. Corrected zones were calculated by subtracting the size of the wafer (1 cm) from the size of the total zone. Representative zone of inhibition results are shown in Table 7.

Table 7

The Sensitivity of a Broad Range of Microorganisms to Silver* Coated Silicon Wafers		
Organism	Source	Corrected Zone of Inhibition (mm)
<i>Staphylococcus epidermidis</i> RC-455	blood	10
<i>Bacillus licheniformis</i> R-2138	tibia	6
<i>Corynebacterium sp</i> R-594	leg	10
<i>Listeria monocytogenes</i> R-590	blood	5
<i>Enterococcus faecalis</i> SR-113	bone	5
<i>Streptococcus bovis</i> SR-62	blood	10
<i>Escherichia coli</i> R-1878	urine	11
<i>Klebsiella ozonae</i> R-308/90	abdomen	10
<i>Enterobacter cloacae</i> R-1682	unknown	8
<i>Proteus vulgaris</i> 3781	urine	4
<i>Providencia stuartii</i> U-3179	urine	8
<i>Citrobacter freundii</i> U-3122/90	urine	7
<i>Salmonella typhimurium</i> ER-1154	urine	6
<i>Serratia marcescens</i> R-850	sputum	6
<i>Pseudomonas aeruginosa</i> U-3027	urine	10
<i>Xanthomonas maltophilia</i> 90-10B	unknown	9
<i>Aeromonas caviae</i> R-1211	wound	5
<i>Branhamella catarrhalis</i> R-2681	unknown	12

Silver deposition*

Example 13

This example demonstrates the use of tantalum as an adhesive layer for coatings of this invention. Tantalum is well known as a material which, in the form of an interlayer, improves adhesion of thin films to substrates. In this example test sections including a group of stainless steel (316) (1 x 1 cm) and silicon (1.7 X 0.9 cm) coupons and sections of latex tubing (5 cm) were cleaned in ethanol and then half of the test sections were coated (by sputtering) with a thin layer (approx. 100 Angstroms) of Ta before an antimicrobial silver film was deposited on them. The second group of the test sections were only coated with the antimicrobial Ag film. Coating conditions are listed below. While all test sections

had similar antimicrobial activity, the Ta coated test sections had much better adhesion properties than did the untreated test sections. Adhesion properties were determined using ASTM method D3359-87, a standard test method for measuring adhesion.

Sputtering Conditions	
Target:	99.99% Ta
Working Gas:	99/1 wt% Ar/O ₂
Working Gas Pressure:	1.3 Pa (10 mTorr)
Power:	0.5 kW
Cathode/Anode Distance:	100 mm
Substrate Temperature:	20°C
Target:	99.99% Ag
Working Gas:	99/1 wt% Ar/O ₂
Working Gas Pressure:	5.3 Pa (40 mTorr)
Power:	0.5 kW
Cathode/Anode Distance:	100 mm
Substrate Temperature:	20°C

Example 14

DC magnetron sputtering was used to deposit silver from a 99.98% pure cathode onto silicon and alumina wafers with commercial argon moisturized with water as the working gas. The argon was moisturized by passing it through two flasks containing 3 litres of room temperature water and one empty flask set up with glass wool to absorb any free liquid before the gas entered the sputtering unit.

The conditions of sputtering and the results of the standard zone of inhibition test performed on the sputtered silver films are shown below. Silver films which normally had no antimicrobial properties when deposited using argon that had not been treated with water yielded a corrected zone of inhibition of up to 8 mm when sputtered using a argon/water vapour mixture as the working gas.

Table 8

Conditions used for DC Magnetron Sputtering of Anti-Microbial Coatings					
Working Gas	Working Gas Pressure Pa (mTorr)	Power	Substrate Temperature	Anode/Cathode Distance	Corrected ZOI
Commercial Argon	1.3 (10)	0.5kW	-10°C	100 mm	0 mm
Ar passed through H ₂ O	1.3 (10)	0.5kW	-10°C	100 mm	8 mm

All publications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

The terms and expressions in this specification are used as terms of description and not of limitation. There is no intention, in using such terms and expressions, of excluding equivalents of the features illustrated and described, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

Claims

1. A modified material comprising:

one or more metals in a form characterized by sufficient atomic disorder such that the material, in contact with a solvent for the material, releases atoms, ions, molecules or clusters containing at least one metal at an enhanced rate relative to its normal ordered crystalline state.

- 5 2. The material as set forth in claim 1, wherein the metal is released on a sustainable basis.
3. The material as set forth in claim 1 in the form of a powder or foil.
4. The material as set forth in claim 1 in the form of a coating.
- 10 5. The material as set forth in claim 3, wherein the material is cold worked to create the atomic disorder.
6. The material as set forth in claim 4, wherein the material is formed by vapour deposition.
- 15 7. The material as set forth in claim 6, wherein the material is formed by physical vapour deposition.
8. A modified antimicrobial material comprising:

20 one or more antimicrobial metals in a form characterized by sufficient atomic disorder such that the material, in contact with an alcohol or water based electrolyte, releases atoms, ions, molecules and clusters of at least one anti-microbial metal into the alcohol or water based electrolyte at a concentration sufficient to provide a localized anti-microbial effect on a sustainable basis.
- 25 9. The material as set forth in claim 8, wherein the metal is selected from the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi, and Zn or an alloy or compound thereof.
10. The material as set forth in claim 8, wherein the metal is Ag, Au or Pd or an alloy or compound of one or more of these metals.
- 30 11. The material as set forth in claim 8 in the form of a powder or foil.
12. The material as set forth in claim 8 in the form of a coating.
13. The material as set forth in claim 11 or 12, in a crystalline form.
- 35 14. A method of forming a modified material containing one or more metals, said method comprising:

40 creating atomic disorder in the material under conditions which limit diffusion such that sufficient atomic disorder is retained in the material to provide release of atoms, ions, molecules or clusters of at least one of the metals into a solvent for the material at an enhanced rate relative to its normal ordered crystalline state.
15. The method as set forth in claim 14, wherein the metal is released on a sustainable basis.
16. The method as set forth in claim 14 wherein the material is a powder or foil of one or more of the metals, and
45 wherein the atomic disorder is formed by cold working of the powder or foil.
17. The method as set forth in claim 16, wherein the powder or foil is worked at a temperature below the recrystallization temperature for the powder or foil to retain atomic disorder.
- 50 18. The method as set forth in claim 17, wherein the material is a nanocrystalline powder.
19. The method as set forth in claim 17, wherein at least one of the metals is an anti-microbial metal and wherein the material is formed with sufficient atomic disorder that atoms, ions, molecules or clusters of the antimicrobial metal are released at a concentration sufficient to provide a localized anti-microbial effect on a sustainable basis.
- 55 20. The method as set forth in claim 19, wherein at least one of the metals is selected from the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi and Zn or alloys or compounds of one or more of these metals.

21. The method as set forth in claim 19, wherein at least one of the metals is Ag, Au or Pd or an alloy or compound containing one or more of these metals.

22. The method as set forth in claim 19, wherein at least one of the metals is silver or an alloy or compound containing silver.

23. The method as set forth in claim 14, wherein the material is formed as a coating on a substrate by vapour deposition under conditions which limit diffusion during deposition and which limit annealing or recrystallization following deposition.

24. The method as set forth in claim 23, wherein the material is formed by physical vapour deposition.

25. The method as set forth in claim 24, wherein the material is a coating of one or more of the metals formed on a substrate by vacuum evaporation, sputtering, magnetron sputtering or ion plating.

26. The method as set forth in claim 25, wherein the deposition is performed under conditions such that the ratio of the temperature of the substrate to the melting point of the metal or metal compound being deposited is maintained at less than about 0.5.

27. The method as set forth in claim 26 wherein the ratio is maintained at less than about 0.3.

28. The method as set forth in claim 26, wherein the deposition is performed such that the angle of incidence of the coating flux on the substrate to be coated is less than about 75°.

29. The method as set forth in claim 26, wherein the deposition is performed by arc evaporation at an ambient or working gas pressure of greater than about 0.001 Pa (0.01 mT).

30. The method as set forth in claim 26, wherein the deposition is performed by gas scattering evaporation at a working gas pressure of greater than about 3 Pa (20 mT).

31. The method as set forth in claim 26, wherein the deposition is performed by sputtering at a working gas pressure of greater than about 10 Pa (75 mT).

32. The method as set forth in claim 26, wherein the deposition is performed by magnetron sputtering at a working gas pressure of greater than about 1.0 Pa (10 mT).

33. The method as set forth in claim 26, wherein the deposition is performed by magnetron sputtering at a working gas pressure of at least 4 Pa (30 mT).

34. The method as set forth in claim 26, wherein the deposition is performed by ion plating at a working gas pressure of greater than about 30 Pa (200 mT).

35. The method as set forth in claim 25, wherein at least one of the metals is an anti-microbial metal and wherein the material is formed with sufficient atomic disorder that atoms, ions, molecules or clusters of the anti-microbial metal are released at a concentration sufficient to produce a localized antimicrobial effect on a sustainable basis.

36. The method as set forth in claim 26, 28 or 32, wherein at least one of the metals is an anti-microbial metal and wherein the material is formed with sufficient atomic disorder that atoms, ions, molecules or clusters of the anti-microbial metal are released at a concentration sufficient to produce a localized anti-microbial effect on a sustainable basis.

37. The method as set forth in claim 25, wherein a composite coating is formed by co-, sequentially or reactively depositing a first metal in a matrix with atoms or molecules of a different material from the first metal such that atomic disorder is created in the matrix.

38. The method as set forth in claim 37, wherein the first metal is an antimicrobial metal and wherein the different material is atoms or molecules either reactively deposited into the matrix from the working gas atmosphere during deposition, or is selected from oxides, nitrides, carbides, borides, sulphides and halides of an inert biocompatible

metal.

39. A method of forming an anti-microbial coating on a device intended for use in contact with an alcohol or water-based electrolyte, comprising:

depositing a coating containing an anti-microbial metal on the surface of the device by vapour deposition to provide a thin film of the metal having atomic disorder such that the coating, in contact with an alcohol or a water-based electrolyte, releases ions, atoms, molecules or clusters into the alcohol or water-based electrolyte at a concentration sufficient to provide a localised anti-microbial effect on a sustainable basis.

40. The method as set forth in claim 39, wherein the anti-microbial effect is sufficient to generate a zone of inhibition, as described in the disclosure, of greater than 5 mm.

41. The method as set forth in claim 39 or 40, wherein the deposition is performed by a physical vapour deposition technique selected from vacuum evaporation, sputtering, magnetron sputtering or ion plating, under conditions which limit diffusion during deposition and which limit annealing or recrystallization following deposition, and wherein optionally the deposition is performed such that the ratio of the temperature of the surface being coated to the melting point of the metal is maintained at less than about 0.5; and wherein preferably the deposition is performed such that the angle of incidence of the coating flux on the device to be coated is less than about 75°.

42. The method as set forth in claim 41, wherein the deposition is performed by arc evaporation at an ambient or working gas pressure of greater than about 0.001 Pa (0.01 mT); or by gas scattering evaporation at a working gas pressure of greater than about 3 Pa (20 mT); or by sputtering at a working gas pressure of greater than about 10 Pa (76 mT); or by magnetron sputtering at a working gas pressure of greater than about 1.0 Pa (7.6 mT), preferably at least 4 Pa (30.4 mT); or by ion plating at a working gas pressure of greater than about 30 Pa (228 mT).

43. The method as set forth in claim 41 wherein the metal is selected from the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi and Zn or an alloy or compound containing one or more of these metals.

44. The method as set forth in claim 41 wherein the metal is Ag, Au or Pd or an alloy or compound containing one or more of these metals.

45. A medical device intended for use in contact with an alcohol or water-based electrolyte having an anti-microbial coating on its surface, comprising:

a medical device formed of a substantially bioinert structural material; and
an anti-microbial coating formed on the surface of the medical device, said coating being formed from one or more anti-microbial metals, and having sufficient atomic disorder such that the coating, in contact with an alcohol or water-based electrolyte, releases ions, atoms, molecules or clusters of the anti-microbial metal into the alcohol or water based electrolyte at a concentration sufficient to provide a localised anti-microbial effect on a sustainable basis.

46. The medical device as set forth in claim 45, wherein the deposition is performed by a physical vapour deposition technique selected from vacuum evaporation, sputtering, magnetron sputtering or ion plating.

47. The medical device as set forth in claim 45 or 46, wherein the metal is selected from the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi and Zn or alloys or compounds containing one or more of said metals.

48. The medical device as set forth in claim 45 or 46, wherein the metal is Ag, Au or Pd or an alloy or compound containing one or more of these metals.

49. The material as set forth in claim 7, wherein the coating is a composite coating formed from at least one first metal, which is the metal to be released, in a matrix containing atoms or molecules of a different material from the first metal, the atoms or molecules of the different material creating atomic disorder in the matrix.

50. The material as set forth in claim 49, wherein the different material is selected from reacted species of the first metal or metal compound; absorbed or trapped atoms or molecules of oxygen, nitrogen, hydrogen, boron, sulphur and halogen; and a second metal.

51. The material as set forth in claim 50, wherein the first metal is an anti-microbial metal and the different material is either (a) selected from oxides, nitrides, hydrides, halides, borides, and carbides of an anti-microbial or a second metal; and absorbed or trapped atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur and halogen or (b) an oxide, nitride, boride, sulphide, halide or hydride of an inert metal selected from Ta, Ti, Nb, V, Hf, Zn, Mo, Si, and Al.
52. The material as set forth in claim 49, comprising silver oxide, silver metal and optionally absorbed or trapped atoms or molecules containing oxygen nitrogen, hydrogen, boron, sulphur and halogen.
53. The method as set forth in claim 23 or 39 wherein the modified material is a composite coating formed by co-, sequentially or reactively depositing a first or anti-microbial metal in a matrix with atoms or molecules of a different material from the said metal such that the atomic disorder is created in the matrix.
54. The method as set forth in claim 53, wherein the first metal is an anti-microbial metal, eg. silver and wherein the different material is selected from atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur and halogen preferably absorbed or trapped in the matrix from the atmosphere of the vapour deposition.
55. The method as set forth in claim 53 or 54 wherein the first metal is an anti-microbial metal and wherein the different material is an oxide, nitride, carbide, boride, halide, sulphide or hydride of an inert metal selected from Ta, Ti, Nb, V, Hf, Zn, Mo, Si and Al, preferably an oxide of Ta, Ti or Nb.
56. The medical device as claimed in claim 45, wherein the coating is a composite coating formed from the anti-microbial metal in a matrix containing atoms or molecules of a material different from the anti-microbial metal, the atoms or molecules of the different material creating atomic disorder in the matrix.
57. The medical device as set forth in claim 56, wherein the different material is one or more of (a) reacted species of the anti-microbial metal or metal compound; (b) absorbed or trapped atoms or molecules of oxygen, nitrogen, hydrogen, boron, sulphur, and halogen; and (c) an inert metal.
58. The medical device as set forth in claim 56, wherein the different material is one or more of (a) oxides, nitrides, hydrides, halides, borides, and/or carbides and/or sulphides of an anti-microbial or an inert metal, the latter being preferably selected from Ta, Ti, Nb, V, Hf, Zn, Mo, Si and Al and (b) absorbed or trapped atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur or halogen.
59. The medical device as claimed in claim 56, wherein the coating comprises silver oxide, silver metal and optionally absorbed or trapped atoms or molecules containing oxygen or oxygen nitrogen, hydrogen, boron, sulphur or halogen.
60. The medical device as claim in claim 41 or 49, wherein the anti-microbial metal is silver or an alloy or compound containing silver.
61. The medical device as claimed in claim 45, wherein the coating is formed by vapour deposition under conditions which limit diffusion during deposition and which limit annealing or recrystallisation following deposition; or physical vapour deposition, preferably performed under conditions such that a ratio of the temperature of the medical device to the melting point of the metal or metal compound being deposited is maintained at less than about 0.5, most preferably at less than about 0.3; or by vacuum evaporation, sputtering, magnetron sputtering or ion plating of one or more anti-microbial metals formed on the said device.
62. The medical device as claimed in claim 61, wherein, the deposition is performed (a) such that an angle of incidence of the coating flux on the medical device to be coated is less than 75°; and/or preferably (b) by arc evaporation at an ambient or working gas pressure of greater than about 0.01 mT (0.001 PA); or (c) by gas scattering evaporation at a working gas pressure of greater than about 20 mT (2.6 PA); or (d) by sputtering at a working gas pressure of greater than about 75 mT (10 PA); or (e) by magnetron sputtering at a working gas pressure of greater than about 10 mT (1.3 PA), or most preferably greater than about 30 mT (3.95 PA); or (f) by ion plating at a working gas pressure of greater than about 200 mT (26.3 PA).
63. The method as set forth in claim 41 wherein the anti-microbial metal is silver or an alloy or compound containing silver.

64. The method as claimed in claim 39, wherein the coating is a composite coating formed by co-, sequentially or reactively depositing an antimicrobial metal in a matrix with atoms or molecules of a material different from the antimicrobial metal, such that the atoms or molecules of the different material create atomic disorder in the matrix.

5 65. The method as claimed in claim 64, wherein the different material is selected from atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur, or halogen (which may be absorbed or trapped in the matrix from the atmosphere of the vapour deposition) and wherein preferably the anti-microbial metal is silver.

10 66. The method as claimed in claim 64, wherein the different material is an oxide, nitride, carbide, boride, sulphide, halide, or hydride or an inert metal selected from the group consisting of Ta, Ti, Nb, V, Hf, Zn, Mo, Si and Al; and wherein preferably the anti-microbial metal is silver or an alloy or compound containing silver and the different material is an oxide of Ta, Ti or Nb.

15 67. The method as set forth in claim 64, wherein the anti-microbial metal is silver and wherein the different material comprises silver oxide and optionally absorbed or trapped atoms or molecules containing oxygen.

20 68. The method as set forth in claim 41, wherein the deposition is performed either such that the ratio of the temperature of the surface being coated to the melting point of the metal is maintained at less than 0.3, or by magnetron sputtering at a working gas pressure of greater than about 30 mT (11 PA).

Patentansprüche

1. Modifiziertes Material, umfassend:

25 ein oder mehrere Metalle in einer Form, die durch eine ausreichende Atomunordnung gekennzeichnet ist, so daß das Material im Kontakt mit einem mit einem Lösemittel für das Material Atome, Ionen, Moleküle oder Cluster, welche mindestens ein Metall enthalten, mit einer erhöhten Geschwindigkeit im Vergleich zu seinem normalen geordneten kristallinen Zustand freisetzt.

30 2. Material gemäß Anspruch 1, wobei das Metall auf verzögerter Basis freigesetzt wird.

3. Material gemäß Anspruch 1 in Form eines Pulvers oder einer Folie.

35 4. Material gemäß Anspruch 1 in Form einer Beschichtung.

5. Material gemäß Anspruch 3, wobei das Material kalt bearbeitet wird, um die Atomunordnung hervorzurufen.

6. Material gemäß Anspruch 4, wobei das Material durch Dampfabcheidung gebildet wird.

40 7. Material gemäß Anspruch 6, wobei das Material durch physikalische Dampfabcheidung gebildet wird.

8. Modifiziertes antimikrobielles Material, umfassend:

45 ein oder mehrere antimikrobielle Metalle in einer Form, die durch eine ausreichende Atomunordnung gekennzeichnet ist, so daß das Material im Kontakt mit einem Elektrolyten auf Alkohol- oder Wasserbasis Atome, Ionen, Moleküle und Cluster mindestens eines antimikrobiellen Metalls in den Elektrolyten auf Alkohol- oder Wasserbasis mit einer Konzentration freisetzt, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis hervorzurufen.

50 9. Material gemäß Anspruch 8, wobei das Metall aus der Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi und Zn oder eine Legierung oder eine Verbindung davon umfassenden Gruppe gewählt wird.

10. Material gemäß Anspruch 8, wobei das Metall Ag, Au oder Pd oder eine Legierung oder eine Verbindung von einem oder von mehreren dieser Metalle ist.

55 11. Material gemäß Anspruch 8 in Form eines Pulvers oder einer Folie.

12. Material gemäß Anspruch 8 in Form einer Beschichtung.

13. Material gemäß Anspruch 11 oder 12 in kristalliner Form.

14. Verfahren zur Bildung eines ein oder mehrere Metalle enthaltenden modifizierten Materials, wobei das Verfahren folgendes umfaßt:

Erzeugen einer Atomunordnung im Material unter Bedingungen, welche die Diffusion beschränken, so daß eine ausreichende Atomunordnung im Material erhalten wird, um eine Freisetzung von Atomen, Ionen, Molekülen oder Clustern mindestens eines der Metalle in ein Lösungsmittel für das Material mit erhöhter Geschwindigkeit im Vergleich zu seinem normalen geordneten kristallinen Zustand bereitzustellen.

15. Verfahren gemäß Anspruch 14, wobei das Metall auf verzögerter Basis freigesetzt wird.

16. Verfahren gemäß Anspruch 14, wobei das Material ein Pulver oder eine Folie von einem oder mehreren der Metalle ist, und wobei die Atomunordnung durch Kaltbearbeitung des Pulvers oder der Folie gebildet wird.

17. Verfahren gemäß Anspruch 16, wobei das Pulver oder die Folie bei einer Temperatur unterhalb der Rekristallisationstemperatur für das Pulver oder die Folie bearbeitet wird, um die Atomunordnung aufrechtzuerhalten.

18. Verfahren gemäß Anspruch 17, wobei das Material ein nanokristallines Pulver ist.

19. Verfahren gemäß Anspruch 17, wobei mindestens eines der Metalle ein antimikrobielles Metall ist, und wobei das Material mit ausreichender Atomunordnung gebildet so daß Atome, Ionen, Moleküle oder Cluster des antimikrobiellen Metalls in einer Konzentration freigesetzt werden, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis bereitzustellen.

20. Verfahren gemäß Anspruch 19, wobei mindestens eines der Metalle aus der Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi und Zn oder Legierungen oder Verbindungen von einem oder mehreren dieser Metalle umfassenden Gruppe gewählt wird.

21. Verfahren gemäß Anspruch 19, wobei mindestens eines der Metalle Ag, Au oder Pd oder eine Legierung oder Verbindung, die eines oder mehrere dieser Metalle enthält, ist.

22. Verfahren gemäß Anspruch 19, wobei mindestens eines der Metalle Silber oder eine Silber enthaltende Legierung oder Verbindung ist.

23. Verfahren gemäß Anspruch 14, wobei das Material als eine Beschichtung auf einem Substrat mittels Dampfabcheidung unter Bedingungen gebildet wird, welche die Diffusion während der Abscheidung beschränken und welche das Tempern oder Rekristallisieren nach der Abscheidung beschränken.

24. Verfahren gemäß Anspruch 23, wobei das Material durch physikalische Dampfabcheidung gebildet wird.

25. Verfahren gemäß Anspruch 24, wobei das Material eine Beschichtung eines oder mehrerer Metalle ist, die auf einem Substrat mittels Vakuumverdampfung, Sputtern, Magnetron-Sputtern oder Ionenplattierung gebildet wird.

26. Verfahren gemäß Anspruch 25, wobei die Abscheidung unter Bedingungen durchgeführt wird, so daß das Verhältnis der Temperatur des Substrates zum Schmelzpunkt des abzuscheidenden Metalls oder der abzuscheidenden Metallverbindung auf weniger als etwa 0,5 gehalten wird.

27. Verfahren gemäß Anspruch 26, wobei das Verhältnis auf weniger als etwa 0,3 gehalten wird.

28. Verfahren gemäß Anspruch 26, wobei die Abscheidung dergestalt vorgenommen wird, daß der Einfallswinkel des Beschichtungsflusses auf dem zu beschichtenden Substrat weniger als etwa 75° beträgt.

29. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Bogenverdampfung bei einem Umgebungs- oder Arbeitsgasdruck von über etwa 0,001 Pa (0,01 mT) vorgenommen wird.

30. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Gasstreuverdampfung bei einem Arbeitsgasdruck von über etwa 3 Pa (20 mT) vorgenommen wird.

31. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Sputtern bei einem Arbeitsgasdruck von über etwa 10 Pa (75 mT) vorgenommen wird.
32. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Magnetron-Sputtern bei einem Arbeitsgasdruck von über etwa 1,0 Pa (10 mT) vorgenommen wird.
33. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Magnetron-Sputtern bei einem Arbeitsgasdruck von mindestens 4 Pa (30 mT) vorgenommen wird.
34. Verfahren gemäß Anspruch 26, wobei die Abscheidung durch Ionenplattierung bei einem Arbeitsgasdruck von über etwa 30 Pa (200 mT) vorgenommen wird.
35. Verfahren gemäß Anspruch 25, wobei mindestens eines der Metalle ein antimikrobielles Metall ist, und wobei das Material mit ausreichender Atomunordnung gebildet ist, so daß Atome, Ionen, Moleküle oder Cluster des antimikrobiellen Metalls in einer Konzentration freigesetzt werden, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis bereitzustellen.
36. Verfahren gemäß Anspruch 26, 28 oder 32, wobei mindestens eines der Metalle ein antimikrobielles Metall ist, und wobei das Material mit ausreichender Atomunordnung gebildet ist, so daß Atome, Ionen, Moleküle oder Cluster des antimikrobiellen Metalls in einer Konzentration freigesetzt werden, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis bereitzustellen.
37. Verfahren gemäß Anspruch 25, wobei eine Verbundbeschichtung durch gemeinsame, nacheinander erfolgende oder reaktive Abscheidung eines ersten Metalls in einer Matrix mit Atomen oder Molekülen eines vom ersten Metall verschiedenen Materials dergestalt gebildet wird, daß Atomunordnung in der Matrix erzeugt wird.
38. Verfahren gemäß Anspruch 37, wobei das erste Metall ein antimikrobielles Metall ist, und wobei das davon verschiedene Material entweder in die Matrix aus der Arbeitsgasatmosphäre während der Abscheidung reaktiv abgeschiedene Atome oder Moleküle sind oder gewählt ist aus Oxiden, Nitriden, Carbiden, Boriden, Sulfiden und Halogeniden eines inerten biokompatiblen Metalls.
39. Verfahren zur Bildung einer antimikrobiellen Beschichtung auf einer Vorrichtung, die zur Verwendung beim Kontakt mit einem Elektrolyten auf Alkohol- oder Wasserbasis vorgesehen ist, umfassend:
Abscheiden einer ein antimikrobielles Metall enthaltenden Beschichtung auf der Oberfläche der Vorrichtung durch Dampfabscheidung, um einen dünnen Film des Metalls mit Atomunordnung zu erzeugen, so daß die Beschichtung im Kontakt mit einem Elektrolyten auf Alkohol- oder Wasserbasis Ionen, Atome, Moleküle oder Cluster in den Elektrolyten auf Alkohol- oder Wasserbasis mit einer Konzentration freisetzt, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis bereitzustellen.
40. Verfahren gemäß Anspruch 39, wobei der antimikrobielle Effekt ausreicht, um eine Inhibierungszone, wie im Beschreibungsteil dargelegt, von mehr als 5 mm zu erzeugen.
41. Verfahren gemäß Anspruch 39 oder 40, wobei die Abscheidung durch eine physikalische Dampfabscheidungstechnik, gewählt aus Vakuumverdampfung, Sputtern, Magnetron-Sputtern oder Ionenplattierung, unter Bedingungen vorgenommen wird, welche die Diffusion während der Abscheidung beschränken, und welche das Tempern oder die Rekristallisation nach der Abscheidung beschränken, und wobei gegebenenfalls die Abscheidung dergestalt durchgeführt wird, daß das Verhältnis der Temperatur der zu beschichtenden Oberfläche zum Schmelzpunkt des Metalls bei weniger als etwa 0,5 behalten wird; und wobei vorzugsweise die Abscheidung dergestalt vorgenommen wird, daß der Einfallswinkel des Beschichtungsflusses auf die zu beschichtende Vorrichtung weniger als etwa 75° beträgt.
42. Verfahren gemäß Anspruch 41, wobei die Abscheidung durch Bogenverdampfung bei einem Umgebungs- oder Arbeitsgasdruck von über etwa 0,001 Pa (0,01 mT) vorgenommen wird; oder durch Gasstreuverdampfung bei einem Arbeitsgasdruck von über etwa 3 Pa (20 mT); oder durch Sputtern bei einem Arbeitsgasdruck von über etwa 10 Pa (76 mT); oder durch Magnetron-Sputtern bei einem Arbeitsgasdruck von über etwa 1,0 Pa (7,6 mT), vorzugsweise mindestens 4 Pa (30,4 mT); oder durch Ionenplattierung bei einem Arbeitsgasdruck von über etwa 30 Pa (228 mT).

43. Verfahren gemäß Anspruch 41, wobei das Metall aus der Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi und Zn oder eine Legierung oder eine Verbindung, die eines oder mehrere dieser Metalle enthält, umfassenden Gruppe gewählt wird.
44. Verfahren gemäß Anspruch 41, wobei das Metall Ag, Au oder Pd oder eine Legierung oder Verbindung, die ein oder mehrere dieser Metalle enthält, ist.
45. Medizinische Vorrichtung, die zur Verwendung im Kontakt mit einem Elektrolyten auf Alkohol- oder Wasserbasis vorgesehen ist, mit einer antimikrobiellen Beschichtung auf ihrer Oberfläche, umfassend:
 - eine medizinische Vorrichtung, die aus einem im wesentlichen bioinerten Strukturmaterial gebildet ist; und
 - eine antimikrobielle Beschichtung, gebildet auf der Oberfläche der medizinischen Vorrichtung, wobei die Beschichtung aus einem oder mehreren antimikrobiellen Metallen gebildet ist und eine ausreichende Atomunordnung aufweist, so daß die Beschichtung im Kontakt mit einem Elektrolyten auf Alkohol- oder Wasserbasis Ionen, Atome, Moleküle oder Cluster des antimikrobiellen Metalls in den Elektrolyten auf Alkohol- oder Wasserbasis mit einer Konzentration freisetzt, die ausreicht, um einen lokalisierten antimikrobiellen Effekt auf verzögerter Basis bereitzustellen.
46. Medizinische Vorrichtung gemäß Anspruch 45, wobei die Abscheidung mittels einer physikalischen Dampfababscheidungstechnik, gewählt aus Vakuumverdampfung Sputtern, Magnetron-Sputtern oder Ionenplattierung, vorgenommen wird.
47. Medizinische Vorrichtung gemäß Anspruch 45 oder 46, wobei das Metall aus der Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi und Zn oder Legierungen oder Verbindungen, die eines oder mehrere dieser Metalle enthalten, umfassenden Gruppe gewählt wird.
48. Medizinische Vorrichtung gemäß Anspruch 45 oder 46, wobei das Metall Ag, Au oder Pd oder eine Legierung oder Verbindung, die ein oder mehrere dieser Metalle enthält, ist.
49. Material gemäß Anspruch 7, wobei die Beschichtung eine Verbundbeschichtung ist, die aus mindestens einem ersten Metall, welches das freizusetzende Metall ist, in einer Matrix, welche Atome oder Moleküle eines vom ersten Metall verschiedenen Materials enthält, gebildet ist, wobei die Atome oder Moleküle des anderen Materials eine Atomunordnung in der Matrix erzeugen.
50. Material gemäß Anspruch 49, wobei das andere Material gewählt wird aus umgesetzten Spezies des ersten Metalls oder einer Verbindung des ersten Metalls; absorbierten oder eingefangenen Atomen oder Molekülen von Sauerstoff Stickstoff, Wasserstoff Bor, Schwefel und Halogen; und einem zweiten Metall.
51. Material gemäß Anspruch 50, wobei das erste Metall ein antimikrobielles Metall ist und das andere bzw. davon verschiedene Material entweder (a) aus Oxiden, Nitriden, Hydriden, Halogeniden, Boriden und Carbiden eines antimikrobiellen oder eines zweiten Metalls; und absorbierten oder eingefangenen Atomen oder Molekülen, die Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel oder Halogen enthalten, oder aus (b) einem Oxid, Nitrid, Borid, Sulfid, Halogenid oder Hydrid eines aus Ta, Ti, Nb, V, Hf, Zn, Mo, Si und Al gewählten inerten Metalls gewählt wird.
52. Material gemäß Anspruch 49, umfassend Silberoxid, Silbermetall und wahlweise absorbierte oder eingefangene Atome oder Moleküle, die Sauerstoff Stickstoff, Wasserstoff Bor, Schwefel und Halogen enthalten.
53. Verfahren gemäß Anspruch 23 oder 39, wobei das modifizierte Material eine Verbundbeschichtung ist, die durch gemeinsame, nacheinander erfolgende oder reaktive Abscheidung eines ersten Metalls oder antimikrobiellen Metalls in einer Matrix mit Atomen oder Molekülen eines vom ersten Metall verschiedenen Materials dergestalt gebildet wird, daß die Atomunordnung in der Matrix erzeugt wird.
54. Verfahren gemäß Anspruch 53, wobei das erste Metall ein antimikrobielles Metall, z.B. Silber, ist, und wobei das davon verschiedene Material aus Atomen oder Molekülen, die Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel oder Halogen enthalten, welche vorzugsweise in der Matrix aus der Atmosphäre der Dampfababscheidung absorbiert oder eingefangen wurden, gewählt wird.
55. Verfahren gemäß Anspruch 53 oder 54, wobei das erste Metall ein antimikrobielles Metall ist, und wobei das davon

verschiedene Material ein Oxid, Nitrid, Carbid, Borid, Halogenid, Sulfid oder Hydrid eines aus Ta, Ti, Nb, V, Hf, Zn, Mo, Si und Al gewählten inerten Metalls, vorzugsweise ein Oxid von Ta, Ti oder Nb, ist.

- 5 56. Medizinische Vorrichtung gemäß Anspruch 45, wobei die Beschichtung eine Verbundbeschichtung ist, die aus dem antimikrobiellen Metall in einer Matrix, welche Atome oder Moleküle eines von dem antimikrobiellen Metall verschiedenen Materials enthält, gebildet ist, wobei die Atome oder Moleküle des anderen Materials eine Atomunordnung in der Matrix erzeugen.
- 10 57. Medizinische Vorrichtung gemäß Anspruch 56, wobei das andere Material eines oder mehrere von (a) umgesetzten Spezies des/der antimikrobiellen Metalls oder Metallverbindung; (b) absorbierten oder eingefangenen Atomen oder Molekülen von Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel und Halogen; und (c) einem inerten Metall ist.
- 15 58. Medizinische Vorrichtung gemäß Anspruch 56, wobei das andere Material eines oder mehrere von (a) Oxiden, Nitriden, Hydriden, Halogeniden, Boriden und/oder Carbiden und/oder Sulfiden eines antimikrobiellen oder eines inerten Metalls, wobei die letzteren vorzugsweise aus Ta, Ti, Nb, V, Hf, Zn, Mo, Si und Al gewählt werden, und (b) absorbierten oder eingefangenen Atomen oder Molekülen, die Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel oder Halogen enthalten ist.
- 20 59. Medizinische Vorrichtung gemäß Anspruch 56, wobei die Beschichtung Silberoxid, Silbermetall und wahlweise absorbierte oder eingefangene Atome oder Moleküle, die Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel oder Halogen enthalten, umfaßt.
- 25 60. Medizinische Vorrichtung gemäß Anspruch 41 oder 49, wobei das antimikrobielle Metall Silber oder eine Silber enthaltende Legierung oder Verbindung ist.
- 30 61. Medizinische Vorrichtung gemäß Anspruch 45, wobei das Beschichten durch Dampfabscheidung unter Bedingungen, welche die Diffusion während der Abscheidung beschränken und das Tempern oder die Rekristallisation nach der Abscheidung beschränken; oder durch physikalische Dampfabscheidung, vorzugsweise unter Bedingungen durchgeführt, so daß das Verhältnis der Temperatur der medizinischen Vorrichtung zum Schmelzpunkt des abzuscheidenden Metalls oder der abzuscheidenden Metallverbindung bei weniger als etwa 0,5, am meisten bevorzugt bei weniger als etwa 0,3, gehalten wird; oder durch Vakuumverdampfung, Sputtern, Magnetron-Sputtern oder Ionenplattierung eines oder mehrerer antimikrobieller auf der Vorrichtung gebildeter Metalle gebildet wird.
- 35 62. Medizinische Vorrichtung gemäß Anspruch 61, wobei die Abscheidung durchgeführt wird, so daß (a) der Einfallswinkel des Beschichtungsflusses auf die zu beschichtende medizinische Vorrichtung weniger als etwa 75° beträgt; und/oder bevorzugterweise (b) durch Bogenverdampfung bei einem Umgebungs- oder Arbeitsgasdruck von über etwa 0,01 mT (0,001 Pa); oder (c) durch Gasstreuverdampfung bei einem Arbeitsgasdruck von über etwa 20 mT (2,6 PA); oder (d) durch Sputtern bei einem Arbeitsgasdruck von über etwa 75 mT (10 PA); oder (e) durch Magnetron-Sputtern bei einem Arbeitsgasdruck von über etwa 10 mT (1,3 PA), oder am meisten bevorzugt von über etwa 30 mT (3,95 PA); oder (f) durch Ionenplattierung bei einem Arbeitsgasdruck von über etwa 200 mT (26,3 PA).
- 40 63. Verfahren gemäß Anspruch 41, wobei das antimikrobielle Metall Silber oder eine Silber enthaltende Legierung oder Verbindung ist.
- 45 64. Verfahren gemäß Anspruch 39, wobei die Beschichtung eine Verbundbeschichtung ist, die durch gemeinsame, nacheinander erfolgende oder reaktive Abscheidung eines antimikrobiellen Metalls in einer Matrix mit Atomen oder Molekülen eines von dem antimikrobiellen Metall verschiedenen Materials dergestalt gebildet wird, daß die Atome oder Moleküle des anderen Materials Atomunordnung in der Matrix erzeugen.
- 50 65. Verfahren gemäß Anspruch 64, wobei das andere Material aus Atomen oder Molekülen, die Sauerstoff, Stickstoff, Wasserstoff, Bor, Schwefel oder Halogen enthalten (welche in der Matrix aus der Atmosphäre der Dampfabscheidung absorbiert oder eingefangen sein können) gewählt wird und das antimikrobielle Metall vorzugsweise Silber ist.
- 55 66. Verfahren gemäß Anspruch 64, wobei das andere Material ein Oxid, Nitrid, Carbid, Borid, Halogenid, Sulfid oder Hydrid eines aus der Ta, Ti, Nb, V, Hf, Zn, Mo, Si und Al umfassenden Gruppe gewähltes inertes Metall ist; und worin das antimikrobielle Metall Silber oder eine Silber enthaltende Legierung oder Verbindung und das andere

Material ein Oxid von Ta, Ti oder Nb ist.

67. Verfahren gemäß Anspruch 64, wobei das antimikrobielle Metall Silber ist und worin das andere Material Silberoxid und gegebenenfalls sauerstoffhaltige, absorbierte oder eingefangene Atome oder Moleküle umfaßt.

68. Verfahren gemäß Anspruch 41, wobei die Abscheidung entweder dergestalt durchgeführt wird, daß das Verhältnis der Temperatur der zu beschichtenden Oberfläche zu dem Schmelzpunkt des Metall bei weniger als 0,3 gehalten wird, oder durch Magnetron-Sputtern bei einem Arbeitsgasdruck von mehr als etwa 30 mT (11 PA).

10 Revendications

1. Matériau modifié comprenant:

un ou plusieurs métaux sous une forme caractérisée par un désordre atomique suffisant pour que le matériau libère, au contact d'un solvant du matériau, des atomes, des ions, des molécules ou des clusters contenant au moins un métal, à une vitesse améliorée par rapport à son état cristallin ordonné normal.

2. Matériau selon la revendication 1, dans lequel le métal est libéré de manière prolongée.

3. Matériau selon la revendication 1, sous la forme d'une poudre ou d'une feuille.

4. Matériau selon la revendication 1, sous la forme d'un revêtement.

5. Matériau selon la revendication 3, dans lequel le matériau est traité à froid pour créer le désordre atomique.

6. Matériau selon la revendication 4, dans lequel le matériau est formé par dépôt en phase vapeur.

7. Matériau selon la revendication 6, dans lequel le matériau est formé par dépôt physique en phase vapeur.

8. Matériau anti-microbien modifié comprenant :

un ou plusieurs métaux anti-microbiens sous une forme caractérisée par un désordre atomique suffisant pour que le matériau libère, au contact d'un électrolyte à base alcoolique ou à base aqueuse, des atomes, des ions, des molécules et des clusters d'au moins un métal anti-microbien dans l'électrolyte à base alcoolique ou à base aqueuse, à une concentration suffisante pour offrir, de manière prolongée, un effet anti-microbien localisé.

9. Matériau selon la revendication 8, dans lequel le métal est choisi dans le groupe consistant en Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi et Zn, ou un alliage ou composé de ceux-ci.

10. Matériau selon la revendication 8, dans lequel le métal est Ag, Au, ou Pd ou un alliage ou composé d'un ou plusieurs de ces métaux.

11. Matériau selon la revendication 8, sous la forme d'une poudre ou d'une feuille.

12. Matériau selon la revendication 8, sous la forme d'un revêtement.

13. Matériau selon la revendication 11 ou 12, sous une forme cristalline.

14. Procédé de formation d'un matériau modifié contenant un ou plusieurs métaux, ledit procédé consistant :

à créer un désordre atomique dans le matériau dans des conditions limitant la diffusion, de sorte qu'un désordre atomique suffisant est conservé dans le matériau pour offrir une libération d'atomes, d'ions, de molécules ou de clusters d'au moins l'un des métaux dans un solvant du matériau, à une vitesse améliorée par rapport à son état cristallin ordonné normal.

15. Procédé selon la revendication 14, dans lequel le métal est libéré de façon prolongée.

16. Procédé selon la revendication 14, dans lequel le matériau est une poudre ou une feuille d'un ou plusieurs des métaux et dans lequel le désordre atomique est formé par traitement à froid de la poudre ou de la feuille.
- 5 17. Procédé selon la revendication 16, dans lequel la poudre ou la feuille est traitée à une température inférieure à la température de recristallisation de la poudre ou de la feuille, pour conserver le désordre atomique.
18. Procédé selon la revendication 17, dans lequel le matériau est une poudre nanocristalline.
- 10 19. Procédé selon la revendication 17, dans lequel au moins l'un des métaux est un métal anti-microbien et dans lequel le matériau est formé avec un désordre atomique suffisant pour que des atomes, des ions, des molécules ou des clusters du métal anti-microbien soient libérés à une concentration suffisante pour offrir, de manière prolongée, un effet anti-microbien localisé.
- 15 20. Procédé selon la revendication 19, dans lequel au moins l'un des métaux est choisi dans le groupe consistant en Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi et Zn, ou les alliages et composés d'un ou plusieurs de ces métaux.
21. Procédé selon la revendication 19, dans lequel au moins l'un des métaux est Ag, Au ou Pd ou un alliage ou composé contenant un ou plusieurs de ces métaux.
- 20 22. Procédé selon la revendication 19, dans lequel au moins l'un des métaux est de l'argent ou un alliage ou composé contenant de l'argent.
23. Procédé selon la revendication 14, dans lequel le matériau est formé sous forme de revêtement sur un substrat, par un dépôt en phase vapeur dans des conditions limitant la diffusion lors du dépôt et limitant le recuit ou la recristallisation après dépôt.
- 25 24. Procédé selon la revendication 23, dans lequel le matériau est formé par dépôt physique en phase vapeur.
25. Procédé selon la revendication 24, dans lequel le matériau est un revêtement contenant un ou plusieurs métaux, qui est formé sur un substrat au moyen d'une évaporation sous vide, d'une pulvérisation, d'une pulvérisation par magnétron ou d'un placage ionique.
- 30 26. Procédé selon la revendication 25, dans lequel le dépôt est effectué dans des conditions telles que le rapport de la température du substrat au point de fusion du métal ou du composé métallique en cours de dépôt est maintenu à une valeur inférieure à environ 0,5.
- 35 27. Procédé selon la revendication 26, dans lequel le rapport est maintenu à une valeur inférieure à environ 0,3.
28. Procédé selon la revendication 26, dans lequel le dépôt est effectué de telle manière que l'angle d'incidence du flux de revêtement sur le substrat à revêtir est inférieur à environ 75°.
- 40 29. Procédé selon la revendication 26, dans lequel le dépôt est effectué au moyen d'une évaporation par arc, sous une pression ambiante ou une pression de gaz de traitement supérieure à environ 0,001 Pa (0,01 mT).
- 45 30. Procédé selon la revendication 26, dans lequel le dépôt est effectué au moyen d'une évaporation par diffusion gazeuse, sous une pression de gaz de traitement supérieure à environ 3 Pa (20 mT).
31. Procédé selon la revendication 26, dans lequel le dépôt est effectué par pulvérisation, sous une pression de gaz de traitement supérieure à environ 10 Pa (75 mT).
- 50 32. Procédé selon la revendication 26, dans lequel le dépôt est effectué au moyen d'une pulvérisation par magnétron, sous une pression de gaz de traitement supérieure à environ 1,0 Pa (10 mT).
33. Procédé selon la revendication 26, dans lequel le dépôt est effectué au moyen d'une pulvérisation par magnétron, sous une pression de gaz de traitement d'au moins 4 Pa (30 mT).
- 55 34. Procédé selon la revendication 26, dans lequel le dépôt est effectué au moyen d'un placage ionique, sous une pression de gaz de traitement supérieure à environ 30 Pa (200 mT).

35. Procédé selon la revendication 25, dans lequel au moins l'un des métaux est un métal anti-microbien et dans lequel le matériau est formé avec un désordre atomique suffisant pour que des atomes, des ions, des molécules ou des clusters du métal anti-microbien soient libérés à une concentration suffisante pour produire, de manière prolongée, un effet anti-microbien localisé.

36. Procédé selon la revendication 26, 28 ou 32, dans lequel au moins l'un des métaux est un métal anti-microbien et dans lequel le matériau est formé avec un désordre atomique suffisant pour que des atomes, des ions, des molécules ou des clusters du métal anti-microbien soient libérés à une concentration suffisante pour produire, de manière prolongée, un effet anti-microbien localisé.

37. Procédé selon la revendication 25, dans lequel un revêtement composite est formé par dépôt concomitant, successif ou réactif d'un premier métal dans une matrice contenant des atomes ou des molécules d'un matériau différent du premier métal, de sorte qu'un désordre atomique est créé dans la matrice.

38. Procédé selon la revendication 37, dans lequel le premier métal est un métal anti-microbien et dans lequel le matériau différent est soit constitué d'atomes ou de molécules déposés, par réaction, dans la matrice, lors du dépôt, depuis l'atmosphère gazeuse de traitement, soit choisi parmi les oxydes, les nitrures, les carbures, les borures, les sulfures et les halogénures d'un métal biocompatible inerte.

39. Procédé de formation d'un revêtement anti-microbien sur un dispositif destiné à être mis en contact avec un électrolyte à base alcoolique ou à base aqueuse, consistant :

à déposer un revêtement contenant un métal anti-microbien sur la surface du dispositif, au moyen d'un dépôt en phase vapeur, pour créer un film mince du métal renfermant un désordre atomique tel que le revêtement, au contact d'un électrolyte à base alcoolique ou à base aqueuse, libère de manière prolongée des ions, atomes, molécules ou clusters métalliques dans l'électrolyte à base alcoolique ou à base aqueuse, à une concentration suffisante pour offrir, de manière prolongée, un effet anti-microbien localisé.

40. Procédé selon la revendication 39, dans lequel l'effet anti-microbien est suffisant pour générer une zone d'inhibition, telle que décrite dans la description, supérieure à 5 mm.

41. Procédé selon la revendication 39 ou 40, dans lequel le dépôt est effectué au moyen d'une technique de dépôt physique en phase vapeur choisie parmi l'évaporation sous vide, la pulvérisation, la pulvérisation par magnétron ou le placage ionique, dans des conditions limitant la diffusion lors du dépôt et limitant le recuit ou la recristallisation après dépôt ; dans lequel, le cas échéant, le dépôt est effectué de telle manière que le rapport de la température de la surface en cours de revêtement au point de fusion du métal est maintenu à une valeur inférieure à environ 0,5 ; et dans lequel, de préférence, le dépôt est effectué de telle manière que l'angle d'incidence du flux de revêtement sur le dispositif à revêtir est inférieur à environ 75°.

42. Procédé selon la revendication 41, dans lequel le dépôt est effectué au moyen d'une évaporation par arc, sous une pression ambiante ou une pression de gaz de traitement supérieure à environ 0,001 Pa (0,01 mT) ; ou au moyen d'une évaporation par diffusion gazeuse, sous une pression de gaz de traitement supérieure à environ 3 Pa (20 mT) ; ou par pulvérisation, sous une pression de gaz de traitement supérieure à environ 10 Pa (76 mT) ; ou au moyen d'une pulvérisation par magnétron, sous une pression de gaz de traitement supérieure à environ 1,0 Pa (7,6 mT), de préférence sous une pression de gaz de traitement d'au moins 4 Pa (30,4 mT) ; ou au moyen d'un placage ionique, sous une pression de gaz de traitement supérieure à environ 30 Pa (228 mT).

43. Procédé selon la revendication 41, dans lequel le métal est choisi dans le groupe consistant en Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi et Zn, ou un alliage ou composé contenant un ou plusieurs de ces métaux.

44. Procédé selon la revendication 41, dans lequel le métal est Ag, Au ou Pd ou un alliage ou composé contenant un ou plusieurs de ces métaux.

45. Dispositif médical destiné à être mis en contact avec un électrolyte à base alcoolique ou à base aqueuse et dont la surface est pourvue d'un revêtement anti-microbien, comprenant :

un dispositif médical formé d'un matériau structurel sensiblement bio-inerte ; et
un revêtement anti-microbien formé sur la surface du dispositif médical, ledit revêtement étant formé à partir

d'un ou plusieurs métaux anti-microbiens et renfermant un désordre atomique suffisant pour que le revêtement offre, au contact d'un électrolyte à base alcoolique ou à base aqueuse, une libération prolongée d'ions, d'atomes, de molécules ou de clusters du métal anti-microbien dans l'électrolyte à base alcoolique ou à base aqueuse, à une concentration suffisante pour offrir, de manière prolongée, un effet anti-microbien localisé.

5

46. Dispositif médical selon la revendication 45, dans lequel le dépôt est effectué au moyen d'une technique de dépôt physique en phase vapeur choisie parmi une évaporation sous vide, une pulvérisation, une pulvérisation par magnétron ou un placage ionique.

10

47. Dispositif médical selon la revendication 45 ou 46, dans lequel le métal est choisi dans le groupe consistant en Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi et Zn, ou les alliages ou composés contenant un ou plusieurs desdits métaux.

48. Dispositif médical selon la revendication 45 ou 46, dans lequel le métal est Ag, Au ou Pd, ou un alliage ou composé contenant un ou plusieurs de ces métaux.

15

49. Matériau selon la revendication 7, dans lequel le revêtement est un revêtement composite formé à partir d'au moins un premier métal, qui est le métal à libérer, contenu dans une matrice renfermant des atomes ou molécules d'un matériau différent du premier métal, les atomes ou molécules du matériau différent créant un désordre atomique dans la matrice.

20

50. Matériau selon la revendication 49, dans lequel le matériau différent est choisi parmi des espèces issues de la réaction du premier métal ou composé métallique ; des atomes ou des molécules absorbés ou piégés d'oxygène, d'azote, d'hydrogène, de bore, de soufre et d'halogène ; et un second métal.

25

51. Matériau selon la revendication 50, dans lequel le premier métal est un métal anti-microbien, et le matériau différent est soit (a) choisi parmi les oxydes, nitrures, halogénures, borures et carbures d'un métal anti-microbien ou d'un second métal ; et des atomes ou molécules absorbés ou piégés contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène, soit (b) un oxyde, nitrure, borure, sulfure, halogénure ou hydruure d'un métal inerte choisi parmi Ta, Ti, Nb, V, Hf, Zn, Mo, Si et Al.

30

52. Matériau selon la revendication 49, comprenant de l'oxyde d'argent, de l'argent métal et des atomes ou molécules, éventuellement absorbés ou piégés, contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène.

35

53. Procédé selon la revendication 23 ou 39, dans lequel le matériau modifié est un revêtement composite formé par dépôt concomitant, successif ou réactif d'un premier métal ou métal anti-microbien dans une matrice contenant des atomes ou molécules d'un matériau différent du premier métal, de sorte qu'un désordre atomique est créé dans la matrice.

40

54. Procédé selon la revendication 53, dans lequel le premier métal est un métal anti-microbien, par exemple l'argent, et dans lequel le matériau différent est choisi parmi les atomes ou molécules contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène qui ont, de préférence, été absorbés ou piégés dans la matrice depuis l'atmosphère de dépôt de vapeur.

45

55. Procédé selon la revendication 53 ou 54, dans lequel le premier métal est un métal anti-microbien et dans lequel le matériau différent est un oxyde, nitrure, carbure, borure, halogénure, sulfure ou hydruure d'un métal inerte choisi parmi Ta, Ti, Nb, V, Hf, Zn, Mo, Si et Al, de préférence un oxyde de Ta, Ti ou Nb.

50

56. Dispositif médical selon la revendication 45, dans lequel le revêtement est un revêtement composite formé à partir du métal anti-microbien dans une matrice contenant des atomes ou des molécules d'un matériau différent du métal anti-microbien, les atomes ou molécules du matériau différent créant un désordre atomique dans la matrice.

55

57. Dispositif médical selon la revendication 56, dans lequel le matériau différent est constitué par un ou plusieurs éléments parmi les suivants : (a) des espèces issues de la réaction du premier métal anti-microbien ou composé métallique ; (b) des atomes ou des molécules absorbés ou piégés d'oxygène, d'azote, d'hydrogène, de bore, de soufre et d'halogène ; et (c) un métal inerte.

58. Dispositif médical selon la revendication 56, dans lequel le matériau différent est constitué par un ou plusieurs élé-

ments parmi les suivants : (a) les oxydes, nitrures, hydrures, halogénures, borures et/ou carbures et/ou sulfures d'un métal anti-microbien ou d'un métal inerte, ce dernier étant de préférence choisi parmi Ta, Ti, Nb, V, Hf, Zn, Mo, Si et Al et (b) des atomes ou molécules absorbés ou piégés contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène.

- 5 59. Dispositif médical selon la revendication 56, dans lequel le revêtement comprend de l'oxyde d'argent, de l'argent métal et, facultativement, des atomes ou molécules absorbés ou piégés contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène.
- 10 60. Dispositif médical selon la revendication 41 ou 49, dans lequel le métal anti-microbien est l'argent ou un alliage ou composé contenant de l'argent.
- 15 61. Dispositif médical selon la revendication 45, dans lequel le revêtement est formé par dépôt en phase vapeur dans des conditions qui limitent la diffusion au cours du dépôt et qui limitent le recuit ou la recristallisation suivant le dépôt ; ou par dépôt physique en phase vapeur, de préférence mis en oeuvre dans des conditions telles que le rapport de la température du dispositif médical au point de fusion du métal ou du composé métallique en cours de dépôt est maintenu à moins d'environ 0,5, de préférence moins d'environ 0,3 ; ou par évaporation sous vide, pulvérisation, ou pulvérisation par magnétron ou plaquage ionique d'un ou plusieurs métaux anti-microbiens formés sur ledit dispositif.
- 20 62. Dispositif médical selon la revendication 61, dans lequel le dépôt est mis en oeuvre (a) de telle sorte que l'angle d'incidence du flux de revêtement sur le dispositif médical à revêtir est inférieur à 75° ; et/ou de préférence (b) au moyen d'une évaporation par arc à la pression ambiante ou à une pression du gaz de traitement supérieure à environ 0,01 mT (0,001 Pa) ; ou (c) au moyen d'une évaporation par diffusion gazeuse à une pression de gaz de traitement supérieure à environ 20 mT (2,6 Pa) ; ou (d) par pulvérisation à une pression de gaz de traitement supérieure à environ 75 mT (10 Pa) ; ou (e) au moyen d'une pulvérisation par magnétron à une pression de gaz de traitement supérieure à environ 10 mT (1,3 Pa), ou de préférence supérieure à environ 30 mT (3,95 Pa) ; ou (f) au moyen d'un plaquage ionique à une pression de gaz de traitement supérieure à environ 200 mT (26,3 Pa).
- 25 63. Procédé selon la revendication 41, dans lequel le métal anti-microbien est l'argent ou un alliage ou composé contenant de l'argent.
- 30 64. Procédé selon la revendication 39, dans lequel le revêtement est un revêtement composite formé par dépôt concomitant, successif ou réactif d'un métal anti-microbien dans une matrice contenant des atomes ou des molécules d'un matériau différent du métal anti-microbien, de telle sorte que les atomes ou molécules du matériau différent créent un désordre atomique dans la matrice.
- 35 65. Procédé selon la revendication 64, dans lequel le matériau différent est choisi parmi les atomes ou molécules contenant de l'oxygène, de l'azote, de l'hydrogène, du bore, du soufre ou un halogène (qui peuvent être absorbés ou piégés dans la matrice depuis l'atmosphère du dépôt en phase vapeur) et dans lequel, de préférence, le métal anti-microbien est l'argent.
- 40 66. Procédé selon la revendication 64, dans lequel le matériau différent est un oxyde, un nitrure, un carbure, un borure, un sulfure, un halogénure ou un hydruire, ou un métal inerte choisi dans le groupe consistant en Ta, Ti, Nb, V, Hf, Zn, Mo, Si et Al ; et dans lequel, de préférence, le métal anti-microbien est l'argent ou un alliage ou composé contenant de l'argent et le matériau différent est un oxyde de Ta, Ti ou Nb.
- 45 67. Procédé selon la revendication 64, dans lequel le métal anti-microbien est l'argent et dans lequel le matériau différent comprend de l'oxyde d'argent et, facultativement, des atomes ou molécules absorbés ou piégés contenant de l'oxygène.
- 50 68. Procédé selon la revendication 41, dans lequel le dépôt est mis en oeuvre soit de telle sorte que le rapport de la température de la surface en cours de revêtement au point de fusion du métal est maintenu inférieur à 0,3, soit au moyen d'une pulvérisation par magnétron à une pression de gaz de traitement supérieure à environ 30 mT (11 Pa).
- 55

THIS PAGE BLANK (USPTO)